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# Aspects of intravenous anaesthesia

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# Aspects of intravenous anaesthesia

# Aspects of intravenous anaesthesia

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## Abstract

**Background:**

Developments in anaesthesia during the recent decades include new drugs with limited unwanted side effects and the need for anaesthesia in new interventions, together with new groups of patients that in the past were considered to be beyond help.

**Aims:**

Study I: To determine the bolus dose of remifentanil that depresses the ventilatory drive as deeply as 1 μg/kg of fentanyl.

Study II: To test the hypothesis that the combination of rocuronium (0.2 mg/kg) with modest doses of propofol and remifentanil during anaesthesia induction always achieves good or excellent intubation conditions in infants.

Study III: To compare the safety of propofol in a large cohort of patients with a known sensitization to soy and/or peanuts to that of non-propofol hypnotic use in a control group.

Study IV: To assess muscular endurance from subparalyzing doses of rocuronium on awake subjects.

**Methods:**

Study I: A randomised, double-blinded, placebo-controlled study in healthy subjects comparing the effect on ventilation of three different doses of remifentanil and one dose of fentanyl.

Study II: A randomised, double-blinded, placebo-controlled clinical trial investigating intubation conditions with and without a low-dose of rocuronium in combination with propofol and remifentanil.

Study III: A retrospective observational cohort study in patients sensitised to peanut and/or soy anaesthetized with either propofol or another anaesthetic agent.

Study IV: A randomised, double-blinded, placebo-controlled study where the effect on muscular endurance of subparalyzing doses of rocuronium was studied in healthy subjects.

**Results:**

A remifentanil bolus of 0.5 μg/kg give similar ventilatory depression as a fentanyl bolus of 1 μg/kg.

Intubation conditions were classified as 'poor' in 14 of 34 (41%) patients given placebo and in 10 of 36 (28%) patients given rocuronium.

There were no identifiable allergic reactions in either the propofol or in the non-propofol group in patients sensitised to soy and/or peanuts.

The sustained handgrip strength after rocuronium (0.08 mg/kg) was one third compared to placebo.

**Conclusions:**

Remifentanil bolus is twice as potent as fentanyl bolus in producing ventilatory depression.

Adding a low-dose rocuronium did not significantly improve intubation conditions compared to placebo.

Propofol was safe to use in a cohort of patients sensitised to soy and/or peanut. Recommendations to withhold propofol because of soy or peanut allergy should be questioned.

Low doses of rocuronium may partly exert its effect by reducing muscular endurance.

Key words: Balanced anaesthesia, intravenous anaesthetics, analgesics opioid - remifentanil, fentanyl, endotracheal intubation, NMBA, rocuronium, neuromuscular monitoring, hypnotics and sedatives, propofol

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# Aspects of intravenous anaesthesia

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*Om vi inte kan göra det enkla rätt –*
*hur ska vi då klara av det svåra?*

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# List of publications

This thesis is based on the following studies, referred to in the text as Study I-IV:

I. Gelberg J, Jonmarker C, Stenqvist O, Werner O
Intravenous boluses of fentanyl, 1 µg kg-1, and remifentanil, 0.5 µg kg-1, give similar maximum ventilatory depression in awake volunteers.
Br J Anaesth. 2012 Jun;108(6):1028-34. doi: 10.1093/bja/aes029

II. Gelberg J, Kongstad L, Werner O
Intubation conditions in young infants after propofol and remifentanil induction with and without low-dose rocuronium.
Acta Anaesthesiol Scand. 2014 Aug;58(7):820-5. doi: 10.1111/aas.12346

III. Gelberg J, Drouget S, Bentzer P, Grubb D
Safety of propofol use in patients allergic to soy or peanut.
Accepted by Eur J Anaesthesiol, awaiting publication

IV. Gelberg J, Bentzer P, Grubb D
Subparalyzing doses of rocuronium reduce muscular endurance without detectable effect on single twitch height
Submitted

# Abbreviations

| | |
|---|---|
| AMG | Acceleromyography |
| CL | Clearance |
| $CO_2$ | Carbon dioxide |
| CV | Coefficient of variation |
| $ED_{95}$ | Effective dose of NMBA to reduce twitch height by 95 % |
| EMG | Electromyography |
| FGF | Fresh gas flow |
| $FiO_2$ | Fraction of inspired oxygen |
| MMG | Mechanomyography |
| NMBA | Non-depolarizing muscle blocking agent |
| n.s. | not significant |
| $PaCO_2$ | Arterial partial pressure of carbon dioxide |
| $PE'CO_2$ | End-tidal partial pressure of carbon dioxide |
| RR | Respiratory rate |
| $SpO_2$ | Peripheral saturation |
| ST | Single twitch |
| $t_{1/2}$ | Terminal half-life time |
| TOF | Train of four stimulation |
| $\dot{V}$ | Minute ventilation |
| VDss | Volume of distribution at steady state |
| Vt | Tidal volume |

Definition of age:

| | |
|---|---|
| Neonate | 0-1 month |
| Infant | 1-12 months |
| Child | 1-18 years |

# Thesis at a glance

| | Aim | Method | Result | Conclusion |
|---|---|---|---|---|
| **Study I** | To determine what intravenous bolus dose of remifentanil that depress ventilatory drive as deeply as 1 µg/kg of fentanyl. | Randomised, double-blinded, placebo-controlled study in healthy subjects. | A remifentanil bolus of 0.5 µg/kg gave similar ventilatory depression as a fentanyl bolus of 1 µg/kg. | Remifentanil bolus is twice as potent as fentanyl bolus in producing ventilatory depression. |
| **Study II** | To test the hypothesis that adding 0.2 mg/kg of rocuronium to propofol and remifentanil would improve intubation conditions. | Randomised, double-blinded, placebo-controlled clinical trial. | Intubation conditions were classified as 'poor' in 14 of 34 (41%) patients given placebo and in 10 of 36 (28%) patients given rocuronium ($p$ = 0.32). | Adding a low-dose rocuronium do not significantly improve intubation conditions compared with placebo. |
| **Study III** | To assess the safety of propofol use in patients sensitised to soy and peanut | A retrospective observational cohort study in patients sensitised to peanut and/or soy anaesthetized with either propofol or another anaesthetic agent. | There were no identifiable allergic reactions in either the propofol or in the non-propofol group. There were no differences in surrogate signs of instability between groups. | Propofol was safe to use in a cohort of patients sensitised to soy and/or peanut. Recommendations to withhold propofol because of soy or peanut allergy should be questioned. |
| **Study IV** | To assess the effect on muscular endurance of subparalyzing doses of rocuronium. | Randomised, double-blinded, placebo-controlled study in healthy subjects. | The sustained handgrip strength after rocuronium was one third compared to placebo ($p$ = 0.008). | Low doses of rocuronium may partly exert its effect by reducing muscular endurance. |

# Introduction

## Background

Developments in anaesthesia during the recent decades include new drugs with limited unwanted side effects and the need for anaesthesia in new interventions, together with new groups of patients that in the past were considered to be beyond help.

Recommendations of how to use new drugs are initially based on research involving healthy volunteers and later on patients with or without any significant organ dysfunction. Sometimes, but not always, studies are conducted on the paediatric population. If not, conclusions are drawn from studies on adults after adjusting for differences in physiology.

With increasing experience using different drugs, new properties can be identified and refined.

At the same time as we are exploring the field and moving the limits, we always have to remember to care for and not to harm the patient.

## Balanced anaesthesia

The concept of balanced anaesthesia dates back to 1910 when George W. Crile introduced his theory of anociassociation. He stated that *"In conscious individuals, all noxious stimuli reach the brain. During general anesthesia only the traumatic stimuli are perceived centrally while with complete anociassociation all stimuli are blocked"* [1]. Crile taught that psychic stimuli associated with surgery could be prevented by light general anaesthesia, while painful stimuli could be blocked by local anaesthesia. The idea of anociassociation became the basis of the intravenous use of opioids. The term "balanced anaesthesia" was later introduced in 1926 by John S. Lundy, who began to supplement inhalation anaesthesia with pentobarbital intravenously and suggested the need for a balance of agents and techniques (e.g., premedication, regional anaesthesia and general anaesthesia with one or more agents) be used to produce the different components of anaesthesia (i.e., analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance

of homeostasis) [2]. The method of providing sleep, pain relief and muscle relaxation, i.e. balanced anaesthesia, with relatively small doses of each separate drug was introduced by Gray and Halton in 1946 [3], whose work opened up possibilities for open heart surgery, new surgical techniques and in a longer perspective, reduced anaesthesia-related morbidity and mortality.

## Remifentanil

Remifentanil hydrochloride is a potent synthetic μ-opioid agonist with an ultrashort action. The drug became commercially available in the United States in 1997 and was launched in Sweden 1 year later. Remifentanil is a 4-anilidopiperidine analogue of fentanyl and undergoes rapid metabolism by blood and tissue esterases. In adult patients remifentanil has a fast clearance (CL; 3 l/min), a small volume of distribution at steady state ($VD_{SS}$; 25 l), a short time-to-peak effect (1.5 min), and a short elimination half-life time ($t_{1/2\beta}$) that is independent of dose and hepatic and renal function [4, 5]. The primary metabolite of remifentanil is the remifentanil acid, GR90291, which is eliminated to a large extent in the urine. Because of a relatively low potency (1:300-1:1000) compared to remifentanil, the metabolite contributes very little to an opioid effect in animals [6].

Remifentanil provides profound analgesia and suppresses airway reflexes, which makes it an attractive drug for sedation and airway procedures [7].

The context-sensitive half-time, the time necessary to achieve a 50 % reduction in the concentration of a drug after termination of a continuous infusion, is very short (approximately 3 min) and independent of the duration of infusion [8]. This in contrast to other opioids, in which the context-sensitive half-time increases with the duration of infusion.

Concomitant administration of propofol decreases the central volume of distribution and CL by 41 % [9]. Consequently, the bolus dose to achieve the target concentration should be reduced, but the infusion rate to maintain the target concentration should be unchanged in the presence of propofol compared to remifentanil alone.

Remifentanil is the first ultrashort-acting opioid that can rapidly be titrated for various levels of surgical stimuli. With predictable pharmacokinetic properties, remifentanil can be useful when rapid onset and offset of opioid effects are desirable, as with short procedures or as in outpatient centres.

The potency of remifentanil has been suggested to be similar to that of fentanyl [10] and approximately 20 times more potent than alfentanil [5].

*Remifentanil in infants and children*

Remifentanil has age-related changes in kinetics that differ from other opioids. The age-related changes in the VDss are similar to the changes that occur with other opioids (i.e., the largest values observed in the youngest age groups), but an inverse relationship between age and CL resulting in no age-related changes in the $t_{1/2\beta}$ of remifentanil. The largest VDss occurs in infants <2 months of age (453 ml/kg) compared to 249 ml/kg in children 7-12 years of age. The CL is more rapid in infants <2 months of age (90.5 ml/min/kg) than in children 7-12 years of age (59.7 ml/min/kg), and the $t_{1/2\beta}$ is 5.4 and 5.3 min, respectively [11].

The remifentanil infusion rate needed to suppress the somatic response to a skin incision in children is twice as high as the corresponding dose in adults in combination with propofol [12]. As in adult patients, remifentanil has been shown to have hemodynamic effects in the paediatric population. Chanavaz et al. [13] found that during sevoflurane anaesthesia in children, remifentanil caused a significant drop in the blood pressure and cardiac index, which was due to a fall in heart rate with no significant change in stroke volume. Pre-treatment with glycopyrrolate or atropine limits the effect on the heart rate.

As with other opioids, remifentanil is a potent respiratory depressant. Children <3 years of age are more tolerant to the effect of remifentanil on the respiratory rate and 50 % of patients receiving a dose of 0.192 μg/kg/min maintain spontaneous ventilation [14] compared to adults in whom equipotent doses are 0.05-0.075 μg/kg/min [15]. This finding could represent the effect of a larger volume of distribution; however, there is an inter-individual variability to consider, despite the predictable plasma half-life time. This variation may be due to a difference in receptor sensitivity [16].

## Rocuronium

In 1942, the muscle relaxant drug, d-tubocurarine (dTc), was reported safe for use in a clinical anaesthesia setting by Griffith and Johnson [17]. Previously, dTc had been used over a number of years to prevent traumatic injuries during electroconvulsive therapy. In the first era of investigating the effects of muscle relaxants, the authors also acted as volunteers. The parameters that were assessed were leg lifting, hand strength as a percentage of normal, abdominal tone and ability to stand. More than a decade later, a six-fold increase in mortality was reported in patients receiving dTc compared to patients who had not received a muscle relaxant [18]. This finding was first ascribed to intrinsic drug toxicity but was later partly explained by a lack of understanding of the pharmacology, residual post-operative muscle paralysis with associated unrecognized respiratory insufficiency and non-

existing guidelines for monitoring muscle strength. The question of how to improve monitoring and safety was raised.

The first report of combining nerve stimulation with the use of muscle relaxant appeared in 1952, when Stephen Thesleff studied the effect of increasing doses of succinylcholine in anaesthetized humans [19].

In 1958, the first commercial neuromuscular monitor (St. Thomas' Hospital Nerve Stimulator) became available. It was claimed that the monitor could distinguish apnoea following succinylcholine from residual anaesthesia.

In 1968, Roberts and Wilson [20] reported the "fade in twitch height" phenomenon after applying four twitches to patients with myasthenia gravis, but it was Ali et al. [21] who first described the use of train-of-four monitoring (TOF) in 1970, for a quantitative assessment of the degree of muscle relaxation after non-depolarizing muscular block in humans.

The first non-depolarizing muscle relaxant agents (NMBAs) were purified from the chondrodendron and other species, which are found in the South American jungle, but newer NMBAs are entirely synthetic.

The potency of an NMBA is commonly expressed by a dose-response relationship, i.e., the dose required to produce an effect. In this case, depression of the twitch height to 50 %, 90 %, or 95 %, is usually expressed as the $ED_{50}$, $ED_{90}$, and $ED_{95}$, respectively. This dose-response relationship is sigmoidal.

The first clinical reports involving rocuronium, a steroidal NMBA classified as an intermediate-acting drug, appeared in 1990 [22]. Most of the drug is taken up by the liver and eliminated via the bile (>70 %), and to a lesser extent by the kidneys. The $ED_{95}$ dose in adults is 0.32 mg/kg [23].

As with other muscle relaxants, the onset and offset time is faster at the laryngeal adductor muscles (the effect site) than at the adductor pollicis muscle in the hand, which is commonly used for monitoring the effect, but the dose required to produce the same degree of muscular block is higher in the larynx, i.e., the laryngeal muscles are less sensitive to NMBAs [24, 25].

*Rocuronium in infants and children*

Trying to understand results from pharmacodynamic studies with rocuronium in children can be confusing. An essential fact is that the ED doses vary between age groups. Potency of rocuronium during balanced anaesthesia is greater in infants than in children and adults with $ED_{95}$ doses of 0.25, 0.41, and 0.35 mg/kg, respectively [26]. Children require more rocuronium to achieve the same level of neuromuscular block as infants and adults. This finding may be due to the growing muscle compartment with a greater number of acetylcholine receptors compared to infants

and adults. The time-to-recovery from equipotent doses are similar between children and adults following one $ED_{95}$ dose of rocuronium; however, other authors claim that recovery from a 1 mg/kg dose is faster in children than in adults [27].

Giving the same dos per kilogram to different groups of patients means that you give different $ED_{95}$ doses, which do have significant impact on the results. Wierda [28] reported a similar time-to-onset after equipotent doses to infants and children, while onset after 0.3 mg/kg is faster in the youngest infants (0-6 months) compared to older infants and children [29].

## Propofol

John B. Glen, a British veterinarian, joined the Imperial Chemistry Industries (ICI) in 1972 to help develop new, short-acting, intravenous anaesthetics.

The standard induction agent at the time was thiopental, which induces anaesthesia quickly, but has limitations. Most prominent among the limitations is accumulation of thiopental. Following intravenous administration, the highly perfused, relatively low-volume tissues, such as the brain, equilibrate rapidly with high-early concentrations of thiopental in the arterial blood, resulting in the induction of anaesthesia. Thiopental concentrations in the blood and highly-perfused tissues then rapidly decrease as the drug redistributes to the large reservoir of less well-perfused lean tissues, such as muscle. When thiopental is administered in large doses, multiple doses or as a continuous infusion, the capacity of the lean tissue to dilute the drug progressively decreases as the tissue concentration approaches equilibrium with the blood. This, together with a long elimination half-life time ($t_{1/2\beta}$; 11.6 hours), sometimes results in an unwanted long recovery [30, 31]. The aim of Glens work was to identify a drug with the anaesthetic potency of thiopental, but with a rapid recovery and characteristics suitable for a continuous infusion to maintain sedation without common unpleasant side-effects, such as nausea and vomiting.

In 1973, Glen demonstrated that one of the tested chemicals, propofol (2, 6-diisopropylphenol), was a promising anaesthetic based on animal tests. Propofol had a rapid onset and could be combined safely with other drugs typically used for sedation. Most importantly, propofol did not accumulate in the body, not even after multiple doses [32].

ICI launched clinical trials, but despite promising results regarding the anaesthetic effects, the ICI experienced a setback with the delivery substance, Cremofor EL (polyethoxylated castor oil), which triggered a life-threatening anaphylactic reaction in several individuals.

Designing an emulsion, a suspension of tiny droplets dispersed in a liquid to carry propofol, was a challenge. This project successfully ended up with a formulation

based on a soybean oil-based emulsion in which propofol retained its useful properties without serious side-effects.

In 1986, the drug received regulatory approval in the UK. The U.S. FDA approval followed in 1989, and it is now approved in more than 90 countries. In 2016, the World Health Organization deemed propofol an "essential medicine" and at that time more than 190 million people had received the drug. John B. Glen was in 2018 awarded the Lasker-DeBakey Clinical Medicine Research Award for his work with propofol.

Propofol exerts a dose-dependent effect by enhancing γ-aminobutyric acid (GABA) induced chloride currents through its binding to the β-subunit of the $GABA_A$ receptor [33]. The pharmacokinetics of the highly protein-bound propofol is best described with a three-compartment model, consisting of a rapidly equilibrating central compartment, a second larger compartment, and a third even larger slowly equilibrating compartment.

The liver is the main site of propofol metabolism and is where the majority of propofol is conjugated and a smaller proportion is hydroxylated. The metabolic clearance of propofol is 1.7 l/min, i.e. ten times as fast as metabolic clearance of thiopental. A number of different cytochrome P450 isoforms are involved in this process. Extrahepatic metabolism in the kidneys and the small intestine accounts for 40 % of propofol clearance [34].

Besides soybean oil, the current propofol formulation consists of glycerol and egg lecithin [35]. Although this drug formulation is considered safe [36], there have since been numerous reports of hypersensitivity reactions [37-43]. In spite of this, the incidence of hypersensitivity reactions to the propofol formulation is estimated to be as low as 1:60 000 exposures, which is half of the estimated incidence of hypersensitivities caused by thiopental (1:30 000) [44]. More recently, a debate has emerged regarding whether patients with food allergies to egg, soy, and peanuts should avoid propofol. This reasoning, however, is only supported by six published case reports with inherent methodological flaws [45-49]. The refined soy oil is unlikely to contain any significant quantities of allergenic particles. The main triggers for egg anaphylaxis are either ovoalbumin, ovomucoid or conalbumin found in the egg white, not the purified egg phosphatide lecithin found in the egg yolk [50, 51]. Peanut allergy is included because of the possibility of cross-reactivity within the legume family [50].

The current level of knowledge results in a frustrating situation because the recommendations, guidelines and product leaflets are not in agreement. Some authors suggest that there are no reasons to avoid propofol in patients allergic to soy and peanuts [44, 51], whereas the product leaflets often warn of propofol use in these patients [52].

Moreover, adding to the confusion, product leaflets differ between countries. In the USA and Australia, egg and soy allergies constitute contraindications, whereas an egg allergy is not a contraindication unlike soy and peanut allergies in UK, Denmark, and Sweden [53, 54]. Nevertheless, the British guidelines advise a ”cautious approach” [55].

*Propofol in infants and children*

The pharmacokinetics of propofol in neonates is variable. Specifically, there is an increased risk for accumulation of propofol due to a markedly reduced clearance during the first weeks of life following a bolus dose or continuous infusion [56]. Clearance of propofol approaches and exceeds adult values between 3 and 12 months of age as the liver and hepatic enzyme systems mature. Because of the increased clearance and larger volumes of distribution, especially the central compartment, higher induction and maintenance doses are required in children <3 years of age to achieve the same blood concentration as adults [57].

The peak effect after a bolus injection occurs later in children (3-11 years of age) than in adults (132 and 80 seconds, respectively). This could be explained by the slower decline in plasma concentrations seen in children which leads to a slower increase of effect site concentration [58].

# Pharmacodynamic studies of neuromuscular blocking agents

There are a large number of reports from clinical trials involving NMBAs. Many of these studies present unique set-ups and designs, making comparisons between studies difficult and sometimes impossible. The results can vary with different patterns of stimulation, frequency and duration of nerve stimulation, recording method and other factors.

During the first decades of muscle relaxant in clinical use, before any neuromuscular monitors were available, hand-grip strength was one of many variables together with head- and leglift and tongue depressor test that were assessed. There are a number of devices to measure hand-grip strength. Hydraulic dynamometers are widely used but a limitation is that they do not provide any information about the endurance and fatigue of hand-grip strength. In addition to measuring peak force, electronic dynamometers also provide you with information such as average grip strength over a set time period and they are also more sensitive to abnormal values such as low grip-strength [59].

Because new muscle relaxants were expected to reach clinical trials in the forthcoming years, an international consensus conference took place in Copenhagen in 1994. As a result of this need, a set of guidelines for Good Clinical Research Practice (GCRP) was published in 1996 [60]. The aim of the guideline process was to achieve a standardisation in research with neuromuscular drugs. These guidelines were updated in 2007 [61].

## Standards common to all types of neuromuscular monitoring

There are usually no problems using surface electrodes as long as the electrodes are placed 3-6 cm apart, but the conducting area should be small (7-11 mm in diameter) to obtain efficient stimulation of the underlying nerve.

The duration of impulses should be 300 μs or less (usually 200 μs) to avoid repetitive nerve firing and direct muscle stimulation.

Because an increased stimulus frequency will shorten the onset time of NMBAs and prolong the duration of action, the same stimulus pattern should be used when measuring onset and duration. Single twitch (ST) stimulation with 0.1 Hz and TOF stimulation have been shown to produce different pharmacodynamic data and are not interchangeable.

Before administration of the muscle relaxant, the response to stimulation should be stable with a variation of not more than 5 % for at least 2 min.

*Equipment*

Mechanomyography (MMG) has for many years been considered the "gold standard" for quantification of neuromuscular block. Today, electromyography (EMG) and acceleromyography (AMG) have replaced MMG in everyday practice. AMG was originally designed as an alternative to MMG because of an easier set-up procedure. It is based on Newton's second law of motion, as follows: force = mass x acceleration. With a constant mass (the thumb for example) the acceleration is directly proportional to the force. The acceleration is measured using a small piezo-electric ceramic wafer. Not all AMG devices are recommended for clinical studies. For example, TOF Watch® and TOF Watch® S from Organon have algorithms making them less useful in this particular setting. TOF Watch® SX, however, does not have this built-in algorithm and can be used in research.

*Stimulation pattern*

In the first set of guidelines, the recommendation when studying onset was to use a 0.1 Hz ST stimulation. This recommendation has in the latest guidelines been revised to use either 0.1 Hz ST or TOF stimulation.

# Endotracheal intubation studies

There are various scoring systems for evaluating intubation conditions in anaesthetized patients. In a number of scoring systems, numerical values have been assigned to qualitative variables, which initially seems appropriate, but the subjective assessments in many situations result in inaccuracies. Instead, a scoring system without numerical values should be used where the frequency distribution of various qualities can be analysed.

In the first guidelines, the following variables were assessed:

- Ease of laryngoscopy
- Position and movement of the vocal cords
- The airway reaction
- Movement of the limbs

In the latest guidelines, the two latter variables have been replaced with "Reaction to intubation," in which only diaphragmatic movement and/or coughing are assessed. For "Excellent intubation conditions," all variables have to be "Excellent." For "Good intubation conditions," all variables have to be either "Excellent" or "Good." The presence of a single "Poor" variable ends up with a clinically unacceptable intubation.

## Intubation without muscle relaxant

Arguments to avoid NMBAs includes short procedures with residual paralysis causing impaired ventilation with decreased hypoxic drive due to inhibition of the carotid body's response to hypoxia [62], risk of anaphylaxis and risk of awareness during general anaesthesia. Reasons not to avoid NMBAs are risks of poor intubation conditions with coughing, oxygen desaturation, increased risk of pulmonary aspiration, and most important, laryngeal injuries [63, 64]. Several studies have shown that using a combination of an intravenous or inhaled hypnotic and an opioid, tracheal intubation can be performed without an NMBA; however, to determine which combination gives the most optimal conditions is difficult. First, there are several possibilities to combine different drugs with different dosages, and the timing and speed of infusion/injection is also of great concern. Second, there is a large variation in the individuals to study.

Generous doses of propofol and remifentanil, when administered consecutively in a short time period during the induction of general anaesthesia, allow technically uncomplicated tracheal intubation to be performed in the majority of adults [65] and children [66-71] (Table 1). Of these studies, there is only one study including infants [68]. Although the two drugs potentiate each other [72], the doses need to be

relatively large. In the majority of cases, an anticholinergic was given. Even though there often were a significant decrease in heart rate and blood pressure no one reported any significant hemodynamic instability, even if an anticholinergic drug was not administered.

**Table 1**
A summary of studies on intubation in children without NMBA

| **Author** | **Batra et al [66]** | | **Blair et al [67]** | | | **Crawford et al [68]** | **Klemola et al [69]** | | **Morgan et al [70]** | **Robinson et al [71]** |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group | 5-10 years | | 3-12 years | | | 2-12 months | 3-9 years | | 2-16 years | 2-12 years |
| Propofol (mg/kg) | 3 | 3 | 3 | 3 | 3 | 4 | 3.5 | 3.5 | 4 | 4 |
| Remifentanil (μg/kg) | 2 | 3 | 1 | 2 | 3 | 3 | 2 | 4 | 1.25 | 1 |
| Clinical acceptable (%) | 50 | 90 | 50 | 69 | 82 | 100 | 90 | 100 | 67 | 80 |
| Atropine/ glycopyrrolat | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Assessment tool | Helbo-Hansen [73] | | Steyn [74] | | | GCRP [60] | Own scoring system | | GCRP [60] | Steyn [74] |
| Significant decrease in heart rate | Yes | Yes | No | No | No | No | Yes | Yes | No | No |
| Significant decrease in blood pressure | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |

# Allergy in anaesthesia

An anaphylactic reaction typically occurs through an Ig-E dependent immunologic mechanism with mast cell degranulation and release of mediators, including histamine, tryptase, leukotrienes, and prostaglandin. These reactions are most commonly triggered by foods, stinging insects venoms or medications. Medications can also trigger anaphylaxis through an Ig-E independent immunologic mechanism (immune complexes activating complements) and through direct mast cell activation [75]. The frequency of life-threatening anaphylactic reactions during anaesthesia has been estimated to range between 1:10 000 and 1:20 000 [76, 77], with a mortality rate of 3-9 % [78]. The severity of perioperative anaphylaxis is greater than anaphylaxis in general. The explanation for the increase in risk is not known but could be a result of a more rapid exposure to culprit medications owing to frequent intravenous medication administration and a delay in recognition and treatment of anaphylaxis. Probably, there is also an increased vulnerability of the affected patient owing to physiologic changes of surgery.

In a multi-centre report from the UK, an Ig E-mediated cause was identified in 64 % of the patients. NMBA constituted the leading cause (38 %) followed by antibiotics (8 %), patent blue dye (6 %), chlorhexidine (5 %) and other agents (7 %). A non-Ig-E mediated cause was attributed in 6 % and no cause could be ascertained in 30 % of the cases [79].

Neuromuscular blocking agents can cause both an IgE-dependent and an IgE-independent anaphylaxis. The tertiary or quaternary ammonium structure is likely responsible for the cross-reactivity among agents and the occurrence of reactions at the first administration. The cross- reactivity also could result in falsely positive skin test results for IgE to neuromuscular blocking agents, resulting in the incorrect attribution of the anaphylaxis to the neuromuscular blocking agent, which is usually not confirmed by challenge [80] .

Induction agents are responsible for no more than 2% of anaphylaxis episodes related to anaesthesia. Induction agents responsible for anaphylaxis are generally barbiturates such as phenobarbital or methohexital. Barbiturates generally cause IgE-dependent reactions. There is some cross-reactivity among the different barbiturates. The nonbarbiturate induction agents, such as benzodiazepines, propofol, etomidate and ketamine, do not generally cause reactions [80].

# Aim

## Study I

The pharmacokinetics of remifentanil, when given as an infusion, is well-documented. Following a long-term infusion with remifentanil, similar plasma concentrations of fentanyl and remifentanil give rise to similar effects [10]; however, situations exist in which an intravenous bolus injection can be useful in spontaneously breathing patients for minor interventions that are associated with intense, but short-lasting pain. Changing the way the drug is administered results in more prominent side effects that must be ascertained.

The aim of the current study was to determine the bolus dose of remifentanil that depresses the ventilatory drive as deeply as 1 μg/kg of fentanyl.

## Study II

By combining propofol and remifentanil with a small dose of a NMBA for intubation, the dose of each drug can be kept low, thus decreasing the risk of hemodynamic depression, yet enabling an early recovery.

The primary hypothesis was that the combination of rocuronium (0.2 mg/kg) with modest doses of propofol and remifentanil during anaesthesia induction always achieves good or excellent intubation conditions in infants. The secondary hypothesis was that the addition of rocuronium to propofol/remifentanil reduced the proportion of poor scores with respect to the individual variables on which the assessment was based. Furthermore, the three-drug combination was expected to ensure intubation at the first attempt.

We also examined the time course of neuromuscular function after rocuronium (0.2 mg/kg).

## Study III

There is a paucity of systematic studies investigating the safety of propofol use in patients with soy and peanut allergies. The previous studies involved a limited number of patients, as well as no control group or confirmatory allergy testing [53, 54, 81-83]. The purpose of this retrospective, observational study was to compare the safety of propofol in a large cohort of patients with a known sensitization to soy and/or peanuts to that of non-propofol hypnotic use in a control group.

## Study IV

Adding low-dose rocuronium (0.1–0.3 mg/kg) to modest doses of propofol and remifentanil has been shown to be a method for successful intubation in some studies [84-86]. It is not clear, however, how low-dose rocuronium exerts its effect because rocuronium does not rely on complete muscle paralysis. We hypothesized that low-dose rocuronium primarily acts by reducing muscular endurance rather than the instantaneous force. The primary objective of this study was to assess muscular endurance from subparalyzing doses of rocuronium on awake subjects. The secondary objective of this study was to calculate the effect of a 0.2 mg/kg dose of rocuronium from the data obtained.

# Material and methods

## Ethical consideration

Ethical approval for all four studies was provided by the Ethical Review Board (EPN) of Lund University, Sweden.

Written informed consent was obtained from participants for Study 1 and 4.

Written informed consent was obtained from parents for Study 2.

Approval was provided by the Swedish Medical Products Agency for Study 1, 2 and 4.

Participating subjects in Study 1 were screened for alcohol and drug abuse with the Drug Use Disorders Identification Test (DUDIT) [87] and Alcohol Use Disorders Identification Test (AUDIT) [88].

Study 1, 2 and 4 were conducted according to the Declaration of Helsinki.

## Study conditions

### Study I

Twelve healthy subjects were studied.

The measurement system (Fig. 1) was designed so that the $CO_2$ stimulus during the peak effect would be similar to remifentanil and fentanyl. To verify that this was achieved, we measured the end-tidal $PCO_2$ ($PE'CO_2$), which is used as a proxy for arterial $PCO_2$ ($PaCO_2$) [89, 90]. The main features of the system are analogous to that of a Mapleson D system [91], but there is no excess valve and instead of an anaesthesia bag, the reservoir consists of a 490 cm long, 30 mm wide open-ended tube with an internal volume of 3.5 litres. The apparatus dead-space (95 ml) between the patient and the fresh gas inlet contains a mouth piece, a heat-moisture exchanger, a flowmeter and a sampling port for $CO_2$ measurement. Signals representing airway flow and airway $PCO_2$ were generated with the S/5 modular monitoring system (GE Healthcare, Helsinki, Finland). Flow was obtained by side-stream spirometry based

on an augmented Pitot methodology [92]. Airway $PCO_2$ was analysed with a side-stream infrared gas analyser with a 95 % response time of 360 ms. The two signals were digitally converted at a rate of 25 Hz. The $PCO_2$ signal was calibrated with 5.0 % $CO_2$ in oxygen and the airway flow signal with an air-filled super-syringe, the plunger of which was moved back and forth to generate known 'tidal' volumes. Zero calibration of both signals was automatically renewed during the recordings.

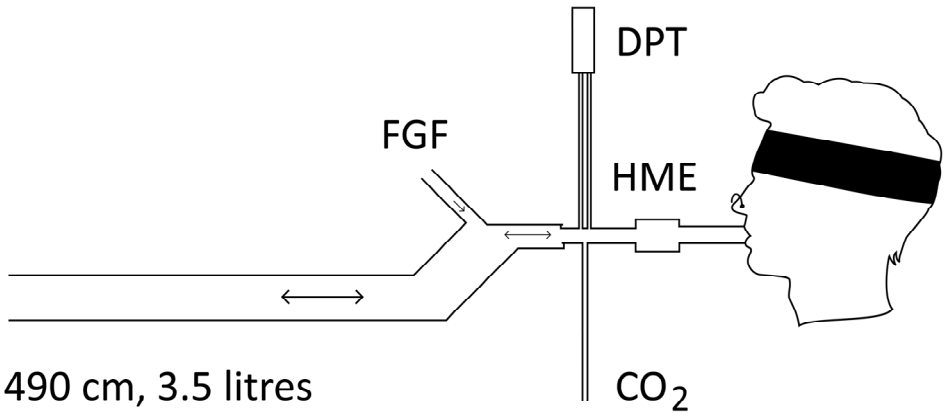


**Figure 1.**
The subject breathed through a mouthpiece, a heat-moisture exchanger (HME) and a resistance connected to a differential pressure transducer (DPT), which measured airway flow. Airway $PCO_2$ was obtained via a sampling line. An open-ended 30 mm internal diameter flexible tube served as reservoir. The apparatus deadspace between the point of entry of the fresh gas flow (FGF) and the patient was 95 ml. FGF was initially 225 ml/kg/min and in order to induce $CO_2$ rebreathing it was then reduced to 75 ml/kg/min before injection of opioid.

The subject visited the laboratory on two study days, 1–3 d apart. On a study day, the effect of fentanyl (1 µg/kg) and placebo or three doses of remifentanil (0.25, 0.5, and 1.0 µg/kg) and placebo were recorded. The fentanyl/placebo day and the remifentanil/placebo day were randomly sequenced. The investigator knew whether or not it was a fentanyl or remifentanil day, but the order between injections on any given day was random and double-blind. Drugs were prepared in coded syringes by a nurse otherwise not involved in the study with 5 ml of placebo solution (saline) or the same volume of opioid solution. The subject, who had fasted for at least 6 h, was placed in a semi-recumbent position. A catheter was inserted in a cubital vein and a small dose of glycopyrrolate (0.5 µg/kg) was injected to reduce salivation. Pulse-oximetric saturation was continuously monitored via a finger probe. After providing the subject with a blindfold, ear plugs, and a nose clip, he/she was asked to breathe through the mouthpiece . The oxygen fraction ($FiO_2$) of the air/oxygen fresh gas was initially set at 0.3 and the fresh gas flow (FGF) at 225 ml/kg/min (high FGF). After 10 min, without notifying the subject, the FGF was changed to 75 ml/kg/min and the $FiO_2$ was increased to 0.4 to avoid hypoxia at the time the opioid was going to be injected [93]. Fifteen minutes later, opioid or placebo, followed by a saline flush,

was injected through an extension tubing. The ventilatory effects were measured over the next 15 min. Once a measurement sequence was finished, at least 1.5 h was allowed to pass before starting the next recording.

Because fentanyl can have long-lasting effects, the placebo recordings obtained on fentanyl days were not used. Hence, there were five recordings to analyse for each volunteer (one with fentanyl, three with remifentanil, and the recording with placebo obtained on remifentanil days). Minute ventilation ($\dot{V}$) was measured over the smallest number of whole breaths that spanned a 30-s interval, as one-half the sum of the mean expiratory and mean inspiratory flow. The time for the measurement was recorded as the midpoint of the interval, and $\dot{V}$ was obtained as a continuous curve by sliding the interval forward in 1-s intervals. Respiratory rate (RR) and $PE'CO_2$ were also measured continuously and the tidal volume (Vt) was obtained as $\dot{V}$ /RR. To obtain reference levels with a minimal random variation $\dot{V}$ was measured over two time periods, as follows:

1. $\dot{V}$ at high FGF was defined as the mean of $\dot{V}$ between 6 and 9 min after starting the recording.
2. $\dot{V}$ at preinjection ($\dot{V}$preinj) was defined as the mean of $\dot{V}$ between 5 and 1 min before the injection of opioid or placebo, i.e., 10–14 min after the FGF had been reduced to 75 ml/kg/min.

The five recordings were obtained under identical conditions up to the point of opioid or placebo injection, which allowed the coefficient of variation (CV) at preinjection to be used as a measure of reproducibility. In each subject, the mean value of the five recordings was determined and used when calculating group medians at high FGF and at preinjection. The nadir of the ventilation curve ($\dot{V}$nadir) after injection of opioid was determined by plotting $\dot{V}/\dot{V}$preinj against time (Fig. 2). Minute ventilation at the nadir of the curve (expressed in percent $\dot{V}$preinj) and the time for the nadir were noted.

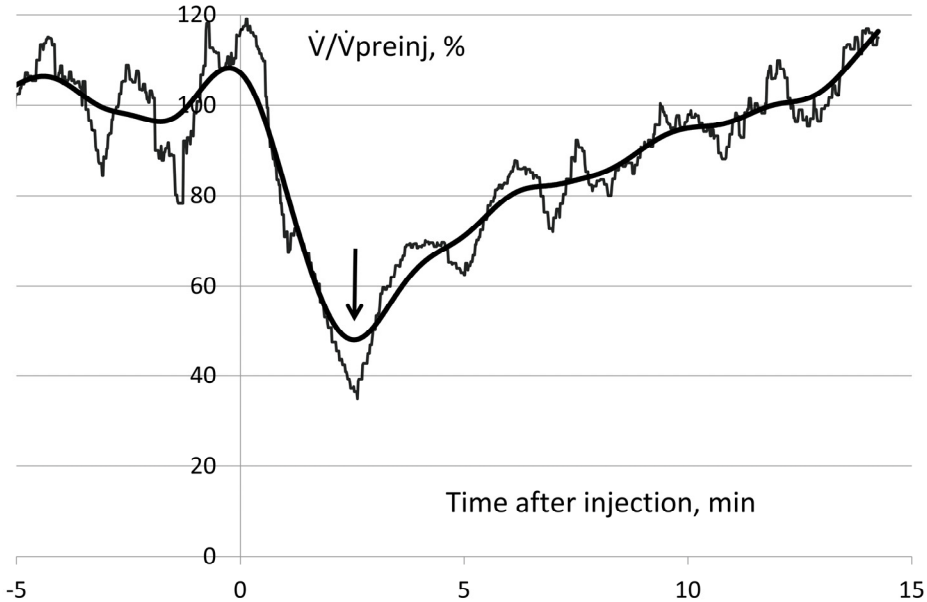


**Figure 2.**
Minute ventilation (V̇), expressed as percentage of pre-injection ventilation (V̇preinj), was plotted against time after injection. A smoothing algorithm was applied, and the value and time V̇nadir (↓) were determined from the smoothed curve. The effect of remifentanil, 0.5 µg/kg, in subject no. 5 is shown. In this case, V̇nadir was 48 % of V̇preinj and occurred 2.5 min after injection.

To determine which remifentanil bolus caused the same degree of respiratory depression as 1 µg/kg of fentanyl, we marked the remifentanil dose on a logarithmic scale and V̇nadir/V̇preinj on a probit scale, and plotted the two measures, thus the two measures were transformed against each other (Fig. 3). The line-of-best-fit was determined by the method of least squares. The V̇nadir/V̇preinj after fentanyl was marked on the line and the equivalent depressant dose of remifentanil was determined. The second, third, and fourth recordings on remifentanil days were analysed to determine whether or not the preceding remifentanil dose had an effect on V̇preinj of the current recording, thus whether or not there was a cross-over effect between recordings.

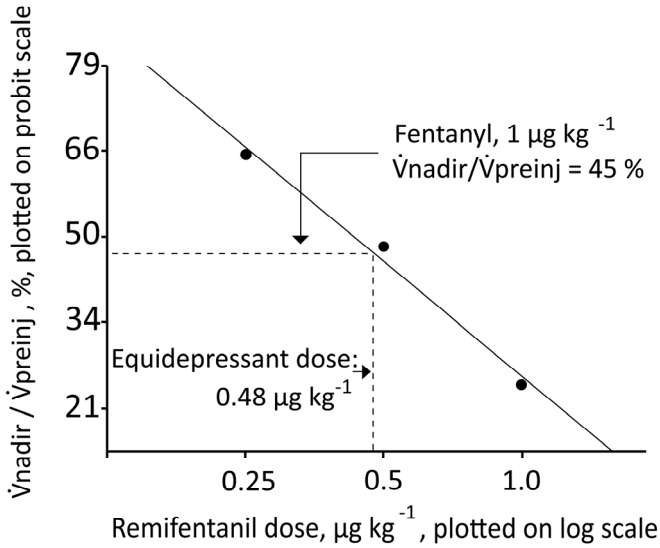


**Figure 3.**
Method for finding the remifentanil dose that gave the same maximum ventilatory depression as 1 µg/kg of fentanyl. In this example (subject no. 5), fentanyl injection resulted in a V̇nadir /V̇preinj of 45%. The equidepressant remifentanil dose was 0.48 µg/kg.

## Study II

Seventy infants American Society of Anesthesiologists (ASA) classification 1–2, 3 weeks to 4 months of age, were included in a study assessing intubation conditions.

Eight infants were included in the study of the neuromuscular response to 0.2 mg/kg of rocuronium.

*Intubation with and without rocuronium*

Randomisation to the rocuronium or placebo group was stratified by age and body weight. After enrolment, a nurse otherwise not involved in administering the anaesthesia, prepared a 1-ml syringe marked "placebo/rocuronium" with placebo (saline) or rocuronium (0.2 mg/kg). If the infant was randomised to receive rocuronium, the syringe was diluted with 0.9 % saline to a total volume of 1 ml. Therefore, all syringes were filled to 1 ml. The group assignment was not known to any of the other participants.

A majority of the infants were administered rectal premedication with midazolam (0.3 mg/kg) 15–20 min before an intravenous catheter was placed in the hand or foot after application of EMLA® (AstraZeneca AB, Södertälje, Sweden). At start of the induction sequence, 0.3 µg/kg of remifentanil was given to decrease the child's reaction while the anaesthetist was positioning the anaesthesia mask. In

infants who did not accept the mask with only remifentanil, 1 mg/kg of Propofol-Lipuro® 10 mg/ml (B. Braun, Melsungen, Germany) was injected, with additional doses of 0.5 mg/kg administered as needed until the mask was accepted. To reduce injection pain from propofol immediately before the first dose of the hypnotic, 1 mg/kg of lidocaine was injected with venous occlusion achieved by a hand-grip around the limb [94]. After 60 s of pre-oxygenation, a concluding dose of propofol was administered. Those infants who had previously received the drug were now given 2 mg/kg; the other infants were given 3 mg/kg. Hence, the total propofol dose was at least 3 mg/kg. Immediately after the concluding propofol dose, 0.2 mg/kg of rocuronium or placebo was injected, followed 15 s later by 2 µg/kg of remifentanil, for a total remifentanil dose of 2.3 µg/kg. The intravenous line was flushed with 5 ml of saline after each injection. The mask was held tightly over the face without ventilating the patient until a laryngoscope was inserted 45 s after the last remifentanil injection, i.e. 1 min after the rocuronium. A 3.0–3.5 orotracheal tube (Sheridan/CF®; Hudson RCI, Temecula, CA, USA) was inserted. All intubations were carried out by the same anaesthetist, who scored intubation conditions according to the guidelines for GCRP (Table 2) [60].

*Time course of neuromuscular blockade*

The procedure for anaesthesia induction was the same as for patients in the main study, except that no relaxant with rocuronium was administered, and the remifentanil dose given during induction was higher (0.3 + 4 µg/kg instead of 0.3 + 2 µg/kg). After tracheal intubation, anaesthesia was maintained with continuous infusions of propofol (10 mg/kg/h) and remifentanil (0.2 µg/kg/min). A neuromuscular function monitor (TOF-Watch® SX; Organon, Ltd., Dublin, Ireland) that analyses the thumb twitch height by AMG during TOF stimulation of the ulnar nerve was connected to skin surface electrodes (Soft-E; Tyco Healthcare, Mansfield, MA, USA). The negative electrode was placed over the nerve on the volar side of one of the wrists and the positive electrode was placed 3 cm proximal to the negative electrode, i.e. on the forearm. The acceleromyography transducer was placed with its largest flat side against the thumb. The other four fingers were immobilised. TOF stimulation was carried out every 15 s. After 2 min with stable measurements, the control twitch height was set to 100 %, and the patient was given 0.2 mg/kg of rocuronium. Twitch heights were recorded until the ratio between the fourth (Tw4) and first (Tw1) twitch heights had surpassed the nadir and recovered to 0.9. Values for Tw1, second-by-second, were obtained through interpolation. In each infant, the time at which Tw4/Tw1 had recovered to 0.9, the time at which Tw1 reached its nadir and the depth of the Tw1 nadir were measured.

**Table 2.**
Assesment of intubation conditions

| | Intubation conditions[a] | | |
|---|---|---|---|
| | Clinically acceptable | | Clinically not acceptable |
| Variables | Excellent | Good | Poor |
| **Laryngoscopy[b] *** | Easy | Fair | Difficult |
| **Vocal cords** | | | |
| Position * | Abducted | Intermediate | Closed |
| Movement * | None | Moving | Closing |
| **Reaction to insertion of tracheal tube and/or cuff inflation** | | | |
| Movement of the limbs * | None | Slight | Vigorous |
| Coughing * | None | Diaphragm | Sustained (>10 s) |

**[a]Intubation conditions**

Excellent: All qualities are excellent
Good: All qualities are either excellent or good
Poor: The presence of a single quality listed under ”poor”

**[b]Laryngoscopy**

Easy: Jaw relaxed, no resistance to blade in the course of laryngoscopy
Fair: Jaw not fully relaxed, slight resistance to blade
Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy

The five ”individual variables”, mentioned in the text, are marked with*.

## Study III

By searching two analytical databases stored in the Department of Immunology at Skåne University Hospital (FlexLab/mikro; Tieto Sweden AB, Stockholm, Sweden; and wwLab; Autonik AB, Sköldinge, Sweden) between 1995 and 2015 (Fig. 4), patients sensitised to soy and/or peanuts were identified. The serum-specific immunoglobulin E (IgE) levels against soy and peanuts were measured using the ImmunoCAP method (Thermo Fisher Scientific, Uppsala, Sweden) and Radioallergosorbent Test (Pharma Diagnostics AB, Uppsala, Sweden). A patient was defined as sensitised if the specific serum IgE level was >0.35 kU/L for soy and/or peanuts [95]. The date of the diagnosis of sensitisation was defined as the date of the analysis.

The sensitised patients were cross-referenced in two surgical management databases (Proviso; Tieto Sweden AB, Stockholm, Sweden and Orbit; EVRY Healthcare Systems AB, Kristianstad, Sweden) stored at Region Skåne, Sweden. A match for a sensitised patient in the surgical management databases was included in the study if the date of the surgical procedure was within 1 year of the date of diagnosis (Fig. 4). The surgical procedures were performed at eight different hospitals throughout Region Skåne.

The anaesthetic charts and the recovery notes of the matching surgical procedures were retrieved and reviewed. All of the drugs given during the anaesthesia and in the recovery room, with the exception for crystalloid fluids, were recorded. Cases were excluded from the study if no intravenous hypnotics were administered. The anaesthetics containing propofol were pooled in the “propofol group” and the anaesthetics completely devoid of propofol were pooled in the “non-propofol group”, which served as the control group (Fig. 4).

Whether or not the patient or next-of-kin reported that the patient was allergic to peanuts and/or soy prior to the anaesthesia was also recorded.

Potential allergic reactions were defined as the presence of at least one of the following criteria: a written comment in the anaesthetic chart or recovery notes of a suspected allergic reaction; a written comment of a typical allergic symptom (cutaneous, respiratory, or cardiovascular manifestations); or the administration of anti-allergic drugs (epinephrine, theophylline, corticosteroids, histamine antagonists, or inhaled bronchodilators) in the presence of hemodynamic and/or respiratory compromise.

The potential allergic reactions were then evaluated by thoroughly scrutinizing the medical record of the anaesthetized patient with special emphasis on allergic follow-up and earlier or later anaesthetics.

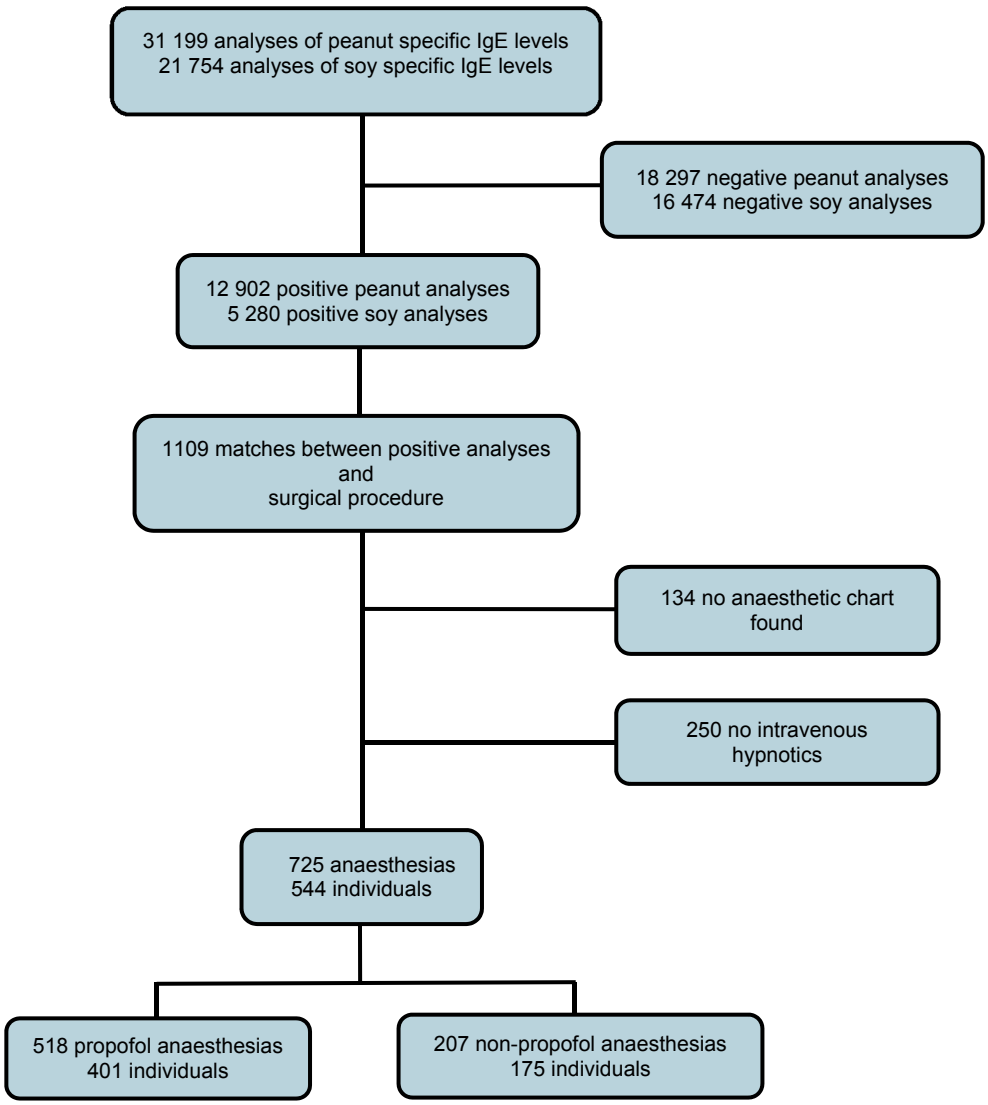


**Figure 4.**
Flow diagram of data acquisition. IgE = Immunoglobulin E.

## Study IV

Eight healthy volunteers were studied.

All subjects visited the laboratory on three different days where the first day was used to acquaint the subjects with the equipment. On the study days, the subjects had fasted for at least six hours before drug administration. Laboratory personnel were fully prepared to take care of any untoward effects of NMBA. The subjects were placed in a modified supine position and blindfolded so that ptosis would not be revealed to the observer. All of the subjects were breathing room air and haemoglobin oxygen saturation was measured using a finger probe. An intravenous catheter was placed in a cubital vein in the non-dominant arm. Syringes were prepared by an assistant nurse not otherwise involved in the study. The syringes contained rocuronium (Esmeron®, 0.04 mg/kg or 0.08 mg/kg; Organon AB, Gothenburg, Sweden) diluted with 0.9 % sodium chloride to a volume of 10 ml or 10 ml of 0.9 % sodium chloride (placebo). The order between injections on the study days was randomized and blinded to the observer and subject. The time between different measurements on both days was at least 90 min to allow for complete recovery of muscular strength.

Day 2 included three measurements of sustained muscular force with an electronic handgrip dynamometer (GRIPPIT; AB Detektor, Gothenburg, Sweden) after administration of placebo, rocuronium 0.04 mg/kg and rocuronium 0.08 mg/kg. The device was automatically calibrated with every set-up. Three minutes after injection, the subject was asked to make a sustained maximum effort with the dominant hand for 80 s while squeezing the dynamometer that had been placed on a table next to the bed. The time interval was based on a reported time to maximum effect of 2.3-3 min after rocuronium doses of 0.15-0.25 mg/kg [24, 26]. The subjects were continuously encouraged by the observer to maintain maximum strength.

Day 3 included two measurements with electric stimulations of the ulnar nerve using surface electrodes (Soft E-Kendall; Tyco Healthcare, Mansfield, MA, USA) after injection of placebo and rocuronium 0.08 mg/kg. The neuromuscular function of the adductor pollicis muscle was monitored with TOF-Watch® SX (Organon AB; Gothenburg, Sweden). ST stimulations were started at a frequency of 0.1 Hz, a duration of 200 µs, and a current of 5 mA. The current was then increased stepwise until the first muscle twitch appeared. Thereafter, the current was further increased by 10 mA. Calibration was performed to set the existing twitch height to 100 % (baseline). After calibration, stimulation was continued for five minutes before injection of placebo and rocuronium. After injection, ST stimulations continued until returning to >90 % of baseline. The stimulations lasted for at least 10 min, but not longer than 30 min after the injection.

*Data analysis*

Data from the handgrip force tests were acquired from the dynamometer using a software program (GrippitDA; AB Detektor, Gothenburg, Sweden) with a sampling rate of 10 Hz. The handgrip force of each subject at every tenth second was calculated as the mean from the 10 data points obtained during 0.5 s before to 0.5 s after every tenth second. For construction of curve profiles over time, the maximum force for each individual reached within the first three seconds during the placebo measurement was set to 100 % and was used as the baseline for calculation of the predicted muscular force at hypothetical 0.2 mg/kg dose of rocuronium.

Data from the ST stimulations were collected from the TOF-Watch® SX Monitor (version 2.2.INT; Organon Ltd., Dublin, Ireland). The evoked muscle response of each subject at every minute was calculated as the mean from the seven data points obtained during 30 s before to 30 s after every minute.

# Statistics

**Study I**

Overall differences between recordings were assessed by repeated-measures analysis of variance on ranks. In the case of statistical significance, Dunnett's method was applied post hoc to assess pair-wise differences. The method states whether $p < 0.05$, that is, it does not give exact $p$-values. Wilcoxon's test was used for the placebo recordings to compare values obtained preinjection with those obtained 15 min postinjection. $P$-values $< 0.05$ were considered to indicate significance.

**Study II**

Between-group differences with respect to proportions were assessed by Fisher's exact test, or when that was not applicable, a $\chi^2$-test. We considered a probability of less than 0.05 to be significant, except when analysing the five individual variables (Table 2). For these variables, the Bonferroni correction was applied, and a $p$-value of $0.05/5 = 0.01$ was considered significant.

**Study III**

Because the ages within groups were not normally distributed, Wilcoxon signed-rank test was used to test for differences in age between groups. The other variables were compared using the $\chi^2$-test. No adjustments for multiple comparisons were made. *P*-values <0.05 indicated statistical significance.

**Study IV**

Statistical comparisons between groups of handgrip force (N) and twitch height (%) were made using Wilcoxon signed-rank test. No adjustments for multiple comparisons were done. The predicted muscular force after a hypothetical 0.2 mg/kg dose of rocuronium at every second from 3 until 60 s was calculated using a generalized linear mixed model in which the logarithmic % force was explained by the dose, time, and an interaction term between dose and time. Only dose levels of 0.04 and 0.08 mg/kg were included in the model. The average curve slope between 3 and 60 s and the *p*-values between curve slopes were generated from the same model with the exception that all dose levels were included and dose was set as a categorical variable. *P*-values <0.05 indicated statistical significance.

# Results

## Study I

*Baseline measurements obtained before opioid/placebo*

Data are presented using median (interquartile range) if not otherwise stated. The measurements were highly reproducible with CV for preinjection values for $PE'CO_2$, $\dot{V}$, and RR of 2.0 (1.6–2.4), 9 (6–12), and 8 (5–10) %, respectively. As expected, changing the FGF from high to low (preinjection) settings had a marked effect; specifically, the $PE'CO_2$ increased by 1.0 (0.8–1.2) to a value of 6.1 (6.0–6.3) kPa, and $\dot{V}$ increased by 6 (4–7) to a value of 14 (13–15) l/min. RR, however, changed by only 0.4 (-0.5 – +2.4) to a value of 13 (10–13) breaths/min. No cross-over effect was discerned with regard to remifentanil. Thus, the dose given during the preceding recording had no effect on current $\dot{V}$preinj ($p$ = 0.39).

*Effects of injection of opioid or placebo*

After each opioid injection, the minute ventilation decreased to a nadir level. The median time for $\dot{V}$ to decrease half-way to the nadir was 1 min after remifentanil and 2 min after fentanyl (Table 3). The $\dot{V}$nadir occurred 4, 3, and 3 min (medians) after remifentanil 0.25, 0.5, and 1 µg/kg, respectively, and 5 min after fentanyl. The median $\dot{V}$nadir/ $\dot{V}$preinj was 51 % after fentanyl 1 µg/kg, which was similar to the value recorded after 0.5 µg/kg of remifentanil (50 %). After the nadir, the $\dot{V}$ curves obtained with 0.25 and 0.5 µg/kg of remifentanil rapidly re-approached the placebo curve (Fig. 5) and at the end of the recording, 15 min after injection, no significant difference versus placebo remained nor was there any significant difference in $PE'CO_2$. In contrast, minute ventilation 15 min after 1 µg/kg of fentanyl (Fig. 5) remained less than the placebo value and also less than values after 0.25 and 0.5 µg/kg of remifentanil ($p$ <0.05; Fig. 5). At that time, the $PE'CO_2$ after fentanyl was 6.5 (6.4–7.0) kPa, significantly greater ($p$ <0.05) than the value after placebo, which was 6.2 (5.8–6.6) kPa.

There was a slow upward trend after placebo, and the $\dot{V}$ at 15 min was 1.6 (1.0–2.9) litres/min greater than at preinjection ($p$ = 0.007). The simultaneous change in $PE'CO_2$ was 0.03 (-0.01 to +0.25) kPa (n.s.).

**Table 3.**
**Summary of ventilatory effects of bolus injections.**
Ventilation nadir is given in percent of the preinjection value. Values are median (interquartile range).

| | V̇nadir/V̇preinj (%) | Time from injection until halfway to nadir (min) | Time from injection until nadir (min) | $PETCO_2$ at nadir (kPa) |
|---|---|---|---|---|
| Fentanyl, 1 µg/ kg | 51 (38-64) | 1.9 (1.5-2.3) | 5.0 (4.4-7.0) | 6.26 (5.98-6.62) |
| Remifentanil | | | | |
| 0.25 µg/kg | 70 (61-77)* | 1.3 (0.8-1.5)* | 3.8 (2.7-4.6)* | 6.18 (6.12-6.50) |
| 0.5 µg/kg | 50 (46-56) | 1.1 (1.0-1.5)* | 2.9 (2.7-3.2)* | 6.11 (5.91-6.45) |
| 1 µg/kg | 29 (24-38)* | 1.2 (1.1-1.4)* | 3.0 (2.7-3.2)* | 6.11 (5.93-6.45) |

*Significant difference in relation to fentanyl *(p* <0.05).

Changes in RR after injection of opioid were small, and with respect to individual recordings, difficult to distinguish from random variation. The mean RR decreased by 1–2 breaths/min to a minima of circa 11/min soon after fentanyl and remifentanil 0.5 and 1 µg/kg, respectively. The minima occurred 2, 2, and 1 min after the injections, respectively. The decrease in RR after remifentanil 0.25 µg/kg was even less pronounced. At 15 min, the median RR was within 0.5 min breaths/min of the placebo value after all four opioid injections. Because of the small changes in RR, Vt and V̇ varied essentially in parallel.

The equal respiratory depressant dose of remifentanil was 0.47 (0.42–0.62) µg/kg when compared with 1 µg/kg of fentanyl. The 95% confidence interval of the mean was 0.44–0.55 µg/kg.

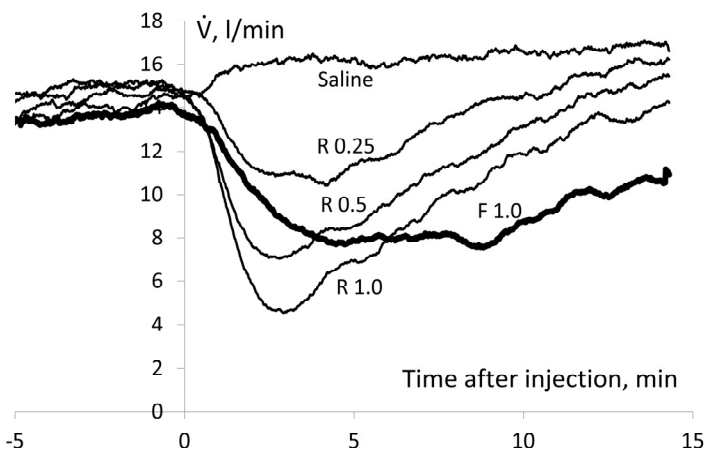


**Figure 5.**
Mean minute ventilation (V̇) curves obtained after injection of fentanyl, 1.0 µg/kg (F 1.0), placebo (saline) and remifentanil, 0.25, 0.5 and 1.0 µg/kg (R 0.25, R 0.5, and R 1.0, respectively).

# Study II

*Intubation with and without rocuronium*

Thirty-four and 36 infants were randomised to receive placebo and rocuronium, respectively. There was no difference in age, weight or pre-medication rate between the groups. The total doses of propofol were 3.0, 3.1–4.0 and 4.1–5.5 mg/kg in 20, 12 and 2 patients, respectively, in the placebo group and in 24, 11 and 1 patient, respectively, in the rocuronium group ($p$ = 0.71). The intubation conditions were poor in 14 of 34 infants (41%) in the placebo group compared with 10 of 36 (28 %) in the rocuronium group ($p$ = 0.32; Table 4). There was no significant between-group difference with respect to any individual variable (Table 4); however, seven infants in the placebo group but only one infant given rocuronium had two or more variables scored as "poor" ($p$ = 0.03; Table 5). Four first attempts at intubation were abandoned in the placebo group compared with none in the rocuronium group ($p$ = 0.051).

**Table 4. Scores in respect of the five individual variables and overall assessment.**

| | **Placebo, *n* = 34** | | | **Rocuronium, *n* = 36** | | | |
|---|---|---|---|---|---|---|---|
| Variable | Excellent | Good | Poor | Excellent | Good | Poor | *p* |
| Laryngoscopy | 27 | 4 | 3 | 31 | 4 | 1 | 0.35 |
| Vocal cords position | 21 | 6 | 7 | 27 | 7 | 2 | 0.08 |
| Vocal cords movement | 20 | 3 | 11 | 30 | 3 | 3 | 0.02 |
| Movement of the limbs | 23 | 8 | 3 | 27 | 8 | 1 | 0.35 |
| Coughing | 14 | 13 | 7 | 24 | 8 | 4 | 0.34 |
| Overall assessment of intubation conditions | 12 | 8 | 14 | 17 | 9 | 10 | 0.32 |

*P* = *p*-value for between-group difference in proportion of "poor" scores. *P*-values regarding individual variables were considered significant if <0.01, see Statistics.

**Table 5.**
Intubation conditions in infants allocated to rocuronium 0.2 mg/kg or placebo.

| **No. of variables scored "poor"** | **No. of infants** | |
|---|---|---|
| | Placebo | Rocuronium |
| None | 20 | 26 |
| One | 7 | 9 |
| Two | 1 | 1 |
| Three | 3 | 0 |
| Four | 2 | 0 |
| All five | 1 | 0 |
| Total | 34 | 36 |

*Time course of neuromuscular blockade after 0.2 mg/kg of rocuronium*

The time course of the height of the first thumb twitch is shown in Fig. 6. The maximum depression of Tw1 occurred 4.3 (2.7–7.7) min after the rocuronium injection and was 82 (47–100) % . Neuromuscular recovery to a Tw4/Tw1 ratio of 0.9 was observed 23 (12–34) min after injection.

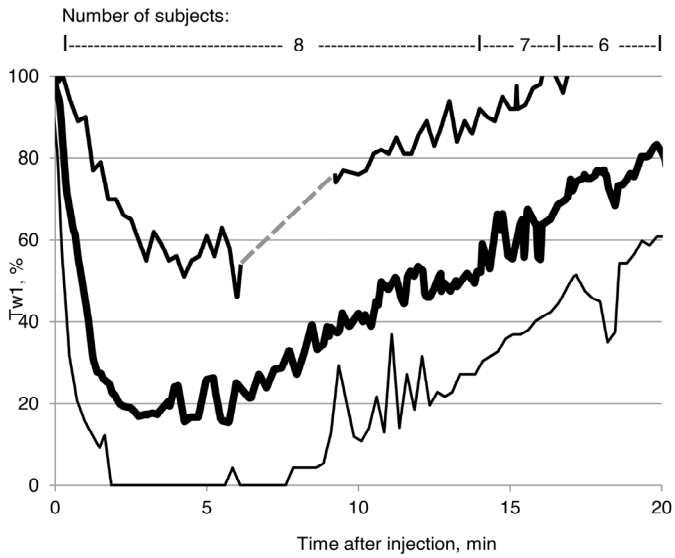


**Figure 6.**
Time course of height of first thumb twitch (Tw1) during train of four ulnar nerve stimulation after injection of rocuronium, 0.2 mg/kg. Tw1 is given in per cent of the preinjection value. Minimum, median (bold) and maximum Tw1 are shown. Dotted line: the curve was interpolated, in order to bridge a probable artefact.

# Study III

The databases stored in the Department of Immunology contained 12 902 positive analyses for peanuts and 5 280 positive analyses for soy in 9 196 individuals between 1995 and 2015 (Fig. 4).

Cross-referencing the sensitised individuals in two databases of surgical procedures yielded 1 109 matches of a surgical procedure within 1 year of diagnosis. In 134 cases, no anaesthetic chart was found. Another 250 cases were excluded because no intravenous hypnotics were administered. Finally, 725 unique anaesthetics of 544 sensitised individuals were included in the study (Fig. 4).

The propofol group consisted of 518 anaesthetics in 401 individuals; 380 (95 %) of these individuals were sensitised to peanuts, 138 (34 %) to soy and 117 (29 %) to both peanuts and soy. The non-propofol group consisted of 207 anaesthetics in 175 individuals; 164 (93 %) of these individuals were sensitised to peanuts, 63 (36 %) to soy and 52 (30 %) to both peanuts and soy (Fig. 4). Thirty-two individuals were present both in the propofol (62 anaesthetics) and in the non-propofol (40 anaesthetics) group.

There were three incidents in the propofol group and two incidents in the non-propofol group that met our criteria for a possible allergic reaction. One incident (propofol group) required administration of epinephrine, but subsequent follow-up and later uneventful propofol-based anaesthesia did not support a drug allergy as a cause. None of the other four possible allergic reactions were followed up with allergen testing. These incidents were judged not to be caused by a drug allergy because the organ manifestations were not treated or were treated with common anaesthesia measures only. The organ manifestations were also either temporally unrelated to a putative drug or more likely explained by a non-allergic untoward effect such as a transient decrease in blood pressure following the administration of a hypnotic drug.

There were no significant differences in the use of anti-allergic drugs, circulatory support drugs and colloid fluids between the groups (Table 6).

**Table 6.**
Miscellaneous peroperative drugs.

| Peroperative drugs – no. (%) | Propofol (*n* = 518) | Non-propofol (*n* = 207) |
|---|---|---|
| **Any antiallergic drug** | **157 (0.30)** | **79 (0.38)** n.s. |
| Corticosteroids | 146 (28.2) | 76 (36.7) |
| Histamine blockers | 3 (0.6) | 1 (0.5) |
| Epinephrine | 1 (0.2) | 0 (0) |
| Inhaled bronchodilators | 3 (0.6) | 1 (0.5) |
| Theophylline | 4 (0.8) | 1 (0.5) |
| **Any circulatory support drug** | **71 (0.14)** | **37 (0.18)** n.s. |
| Atropine | 37 (7.1) | 20 (9.7) |
| Ephedrine | 23 (4.4) | 11 (5.3) |
| Norepinephrine | 9 (1.7) | 5 (2.4) |
| Phenylephrine | 1 (0.2) | 1 (0.5) |
| Dobutamine | 1 (0.2) | 0 (0) |
| **Colloid fluids** | **30 (5.8)** | **12 (5.8)** n.s. |

no. = numbers; n.s. = not significant

There was a significant difference in reported allergies to peanuts and soy between the groups suggesting a tendency to avoid propofol if a peanut or soy allergy was reported (Table 7).

**Table 7.**
Basic data and reported allergies.

| Basic data | Propofol | Nonpropofol |
|---|---|---|
| Anaesthesias - no. | 518 | 207 |
| Individuals - no. | 401 | 175 |
| Women – no. (%) | 173 (43) | 75 (43) |
| Median age (IQR) - yr | 18 (10 – 31) | 13 (6 – 22)*** |
| Reported allergies – no. (%) | | |
| Nuts | 80 (15) | 66 (32)*** |
| Peanuts | 67 (13) | 71 (34)*** |
| Soy | 20 (4) | 48 (23)*** |

no. = numbers, IQR = interquartile range, yr = years, *** = $p < 0.001$

There were significant differences in the total use of inhalational anaesthetics and neuromuscular blockers, but no difference in the use of opioids or local anaesthetics between the groups (Table 8).

**Table 8.**
The most common anaesthetic drugs.

| Anaesthetic drugs – no. (%) | Propofol ($n$ = 518) | Non-propofol ($n$ = 207) |
|---|---|---|
| Propofol | 518 (100) | 0 (0) |
| Thiopental | 22 (4.2) | 194 (93.7) |
| Midazolam | 8 (1.5) | 16 (7.7) |
| Ketamine/esketamine | 1 (0.2) | 3 (1.4) |
| Inhalational anaesthetics | 321 (62.0) | 190 (91.8)*** |
| Muscle relaxants | 180 (34.7) | 119 (57.5)*** |
| Opioids | 445 (85.9) | 184 (88.9) n.s. |
| Local anaesthetics | 226 (43.6) | 85 (41.1) n.s. |

no. = numbers; *** = $p < 0.001$; n.s. = not significant

# Study IV

Data are presented using median (range) if not otherwise stated. The maximum handgrip force was similar in the placebo and 0.04 mg/kg rocuronium group (360 N (198-483) vs. 352 (257-405); $p = 0.945$) and a trend of a lower force was observed in the 0.08 mg/kg rocuronium group compared with placebo (317 N (199-364); $p = 0.055$) (Table 9). Even though the subjects attempted to maintain maximum force, the force gradually decreased to 214 N (120-278) in the placebo group and a slightly lower force in the 0.04 mg/kg rocuronium group (187 N (124-256); $p = 0.016$) at 60 s. In the 0.08 mg/kg rocuronium group, the sustained grip force decreased to approximately one-third compared with placebo (69 N (30-166); $p = 0.008$) (Table 9).

**Table 9.**
Effect of placebo and different doses of rocuronium on sustained force, median (range).

| Time (s) | Placebo (N) | Rocuronium 0.04 mg/kg (N) | Rocuronium 0.08 mg/kg (N) |
|---|---|---|---|
| Max force | 360 (198-483) | 352 (257-405) *n.s.* | 317 (199-364) *n.s.* |
| 10 | 260 (154-363) | 256 (210-316) | 240 (200-342) |
| 20 | 246 (153-298)) | 222 (141-314) | 194 (168-285) |
| 30 | 234 (126-282) | 222 (157-257) | 149 (125-247) |
| 40 | 222 (129-310) | 217 (145-269) | 126 (80-215) |
| 50 | 203 (138-290) | 216 (155-248) | 92 (54-159) |
| 60 | 214 (120-278) | 187 (124-256)* | 69 (30-166)** |
| 70 | 208 (120-254) | 175 (127-218) | 47 (33-127) |

n.s.= not significant; * = $p < 0.05$; ** = $p < 0.01$ as compared with placebo.

The average curve slope was steeper in the 0.08 mg/kg rocuronium group compared with placebo (2.45 % reduction/s, 95 % CI [2.00, 2.90] vs. 0.81 [0.33, 1.29]; $p < 0.001$) but not in the 0.04 mg/kg group (0.76 [0.28-1.24]; $p = 0.873$), indicating a reduced ability to sustain muscular force over time in the 0.08 mg/kg group (Fig. 7).

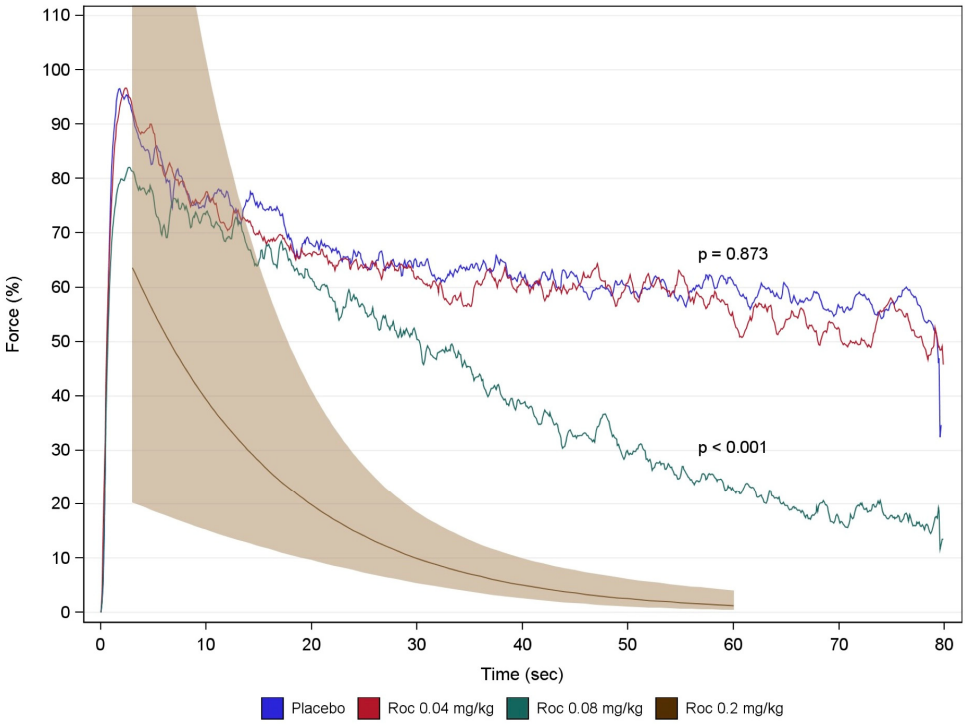


**Figure 7.**
Average handgrip force over time from eight subjects after placebo, rocuronium 0.04 mg/kg and 0.08 mg/kg was given. Subjects started to squeeze the dynamometer three minutes after placebo/rocuronium was given. A predicted curve between three and 60 sec with 95 % confidence interval after a hypothetical dose of rocuronium 0.2 mg/kg is inserted. P-values denote comparisons of average slope with placebo. Placebo curve does not reach 100 % because subjects did not reach maximum at the exact same time point.

Curve modelling generated a predicted muscular force at 60 s of 1.27 %, (95% CI [0.40, 4.03]) after a hypothetical rocuronium dose of 0.2 mg/kg (Figure 7).

Twitch height at the time of injection was similar in the placebo and in the rocuronium group (106 % (95-114) vs. 108 % (92-132); $p = 0.641$). Four min later, there was still no significant difference between groups (105 % (94-119) vs. 100 (85-106); $p = 0.055$; Table 10).

**Table 10.**
Effect of placebo and rocuronium 0.08 mg/kg on twitch height, median (range)

| Time (min) | Placebo (%) | Rocuronium 0.08 mg/kg (%) |
|---|---|---|
| 0 | 106 (95-114) | 108 (92-132) *n.s.* |
| 1 | 105 (94-113) | 103(92-125) |
| 2 | 107 (96-114) | 102 (89-115) |
| 3 | 107 (97-115) | 102 (86-111) |
| 4 | 105 (94-119) | 100 (85-106) *n.s.* |
| 5 | 106 (92-121) | 100 (85-103) |

The currents used for ST stimulation were 22.5 (19-26) mA in the placebo and 23.5 (20-27) mA in the rocuronium group ($p = 0.999$).

# Discussion

## Study I

Half as large a bolus dose of remifentanil was needed to achieve the same maximum respiratory depression as with fentanyl. This finding can be contrasted to the reports by Lang et al. [10] and McEwan and colleagues [96] in which similar plasma concentrations, in ng/ml, of remifentanil and fentanyl gave similar effects. The apparent contrast between the two assessments of equipotency - the first relating the bolus doses of different drugs to each other and the second relating plasma concentrations - can be explained by known differences between the drugs with respect to pharmacokinetics and pharmacodynamics. Thus, it may be predicted that a remifentanil bolus injection will have an earlier and more distinct peak effect than fentanyl [9], which is indeed what we observed (Table 3 and Fig. 5). The difference in onset of remifentanil when comparing the effect on ventilation and the effect on EEG may be related to the fact that ventilatory drive and EEG effect depend on different neural pathways and that local blood flows also may differ, as well as blood-brain barrier characteristics and neural responsiveness to opioids [90, 97, 98]. The respiratory effects of bolus injection of the two drugs have not been directly compared previously.

The mean ventilation started to decrease 15–30 s after opioid injection (Fig. 5). This finding may correspond to a brief interval during which the opioid bolus travelled from the cubital vein to the brain. Babenco and colleagues [89] measured ventilation every 30 s after a 0.5 µg/kg bolus dose of remifentanil. The curve which was generated showed no obvious delay, perhaps due to a coarser time resolution. As judged from their mean data, the midway response occurred between 30 s and 1 min after injection. The onset was nearly as fast as in the present study, with the midway response reached 1 min after the injection, i.e. a minute earlier than with fentanyl (Table 3). In the study by Babenco the nadir of the ventilation curve occurred 2–4 min after injection and the recovery was virtually complete at 15 min (Fig. 6 in [89]), which is consistent with our findings (Table 3 and Fig. 5).

Egan and colleagues [5] administered a fast infusion of remifentanil and found the equilibration half-time between the central compartment and the effect compartment to be 1.6 min. The peak effect occurred after 1.2 min on a simulated curve depicting the anticipated effects of a bolus injection. In the present study, the ventilation nadir

occurred after approximately 3 min. The discrepancy might be explained by the different methods of administering remifentanil, and by the fact that Egan et al. based their assessment on EEG findings and gave total doses >30 µg/kg; i.e. much greater doses than our maximal bolus of 1 µg/kg. Glass and colleagues [99] found that analgesia, assessed as tolerance to tibial pressure, peaked between 1 and 3 min after a short (60 s) remifentanil infusion. The analgesic peak occurred slightly earlier than the ventilation nadir in the present study. In the study by Glass et al., the rate of decline with respect to the analgesic effect (Fig. 2 in [99]) was approximately the same as what we found with respect to the ventilatory effect, and analgesia from remifentanil was no longer present 20 min after 1 and 2 µg/kg.

Our study has several potential limitations. First, the minute ventilation increased by approximately 10 % during the recording after placebo (Fig. 5). This was not due to a significant increase in $PE'CO_2$; the median change in $PE'CO_2$ was only +0.03 kPa. Although we do not have a good explanation for the $\dot{V}$ increase, we do not believe that the $\dot{V}$ increase had an important effect on our findings. Also, several injections were given on remifentanil days, but because subjects rested more than 90 min between recordings and the context-sensitive half-time is <5 min for the drug [100], it is unlikely that residual opioid effects influenced the next recording. In fact, the remifentanil dose given during a recording had no effect on $\dot{V}$preinj of the next recording ($p = 0.39$). It is also unlikely that acute opioid tolerance was a source of error. Gustorff and colleagues [101] administered a 4.8 µg/kg/h infusion for 3 h (14 µg/kg) and found no alteration in the pain threshold . We only administered 1 + 0.5 + 0.25 µg/kg (1.75 µg/kg).

Opioids depress chemosensitive and rhythm-generating centres in the brainstem, thus leading to slowing and irregularity of the respiratory rhythm [102]. A method to avoid this opioid effect when studying effects on ventilation is to apply isocapnic hyperventilation with a constant level of $PCO_2$. This can be arranged by including a rebreathing device into the breathing circuit. The method has also been used to provide a more rapid return of responsiveness after anaesthesia with volatile drugs, both in experimental and clinical settings [103-106].

We chose the present method for $CO_2$ rebreathing because the simplicity should allow for stable and reproducible measurements, which was indeed accomplished, as attested to by the low coefficients of variation for $PE'CO_2$, $\dot{V}$, and RR. The method differs from previous measurement techniques. Babenco and colleagues [89] and Blouin and colleagues [107] used variable $CO_2$ absorption to keep the $PE'CO_2$ constant in spite of a changing minute ventilation, while we relied on the properties of the Mapleson D system to minimize fluctuations in $PaCO_2$ due to variations in ventilation. Therefore, different respiratory stimulation from $CO_2$ was not a confounding factor when we assessed the equivalent depressant dose of remifentanil in relation to fentanyl.

At the end of the 15 min recording, however, the median $PE'CO_2$ was 0.3 kPa higher after fentanyl than after placebo injection. Thus, the $\dot{V}$ recorded at that time (Fig. 5) did not quite reveal the full degree of respiratory depression after fentanyl. During the present experiment, rebreathing gave a continuous respiratory stimulus, whereas the inspired carbon dioxide concentration will be close to zero in most clinical settings. If the respiratory depression has a relatively slow onset, such as is the case after a fentanyl bolus (Fig. 4), the gradual decrease in ventilation may allow $PaCO_2$ time to increase, partly off-setting the ventilatory depressant effect of the opioid itself [108, 109]. With remifentanil, the anaesthetist, who wants the patient's spontaneous breathing to be retained, must assure that the onset of respiratory depression is not too abrupt, for example, by injecting remifentanil in fractionated doses.

We conclude that remifentanil 0.5 µg/kg depressed the ventilatory drive similar to that of fentanyl 1 µg/kg, in awake volunteers. As expected, onset and recovery were faster with remifentanil.

# Study II

The addition of 0.2 mg/kg rocuronium did not significantly ensure good or excellent intubation conditions as compared with no rocuronium, and the primary hypothesis was therefore not confirmed. In addition, the rocuronium did not significantly improve the score with respect to any of the five individual variables that we evaluated when assessing intubation conditions (Table 4). Hence, the secondary hypothesis also remained unconfirmed. The fact that all infants in the rocuronium group were intubated with the first attempt, whereas intubation failed with the first attempt in four infants from the placebo group ($p = 0.051$) suggests that rocuronium had a positive effect. Furthermore, two or more individual variables were scored as poor in only one patient given relaxant compared to seven in the placebo group ($p = 0.03$; Table 5). The combination of propofol, rocuronium and remifentanil used in the study was chosen for a number of reasons. First, we wished to minimize the duration of action of the rocuronium so that pharmacologic reversal would not be needed. Second, Barclay et al. [84] achieved optimal intubation conditions in adults by adding 0.3 mg/kg of rocuronium to a propofol–alfentanil combination that, by itself, produced poor results. In the that study, even 0.1 mg/kg improved intubation conditions, suggesting that an intermediate rocuronium dose might be sufficient in infants; the $ED_{95}$ is approximately 70 % of that in adults [26]. The present findings were therefore unexpected. The most important reason why our expectations and the findings diverged is most likely, that the timing between the three different drugs was not optimal. The thumb twitch response depicted in Fig. 6 suggests that we should have allowed more time for the rocuronium to reach an optimal effect before

attempting intubation; the nadir for Tw1 occurred 4 min (3–8) after the injection, but we waited only 1 min before performing the laryngoscopy. In contrast, the onset time for rocuronium in the laryngeal muscles is faster than the adductor pollicis muscle [110]. The time from bolus injection of the hypnotic and opioid until laryngoscopy was 60–70 s for propofol and 45 s for remifentanil. In adults, the time to peak effect after injection is approximately 80 s for propofol [58] and 1 min for remifentanil [5] when assessed with electroencephalogram. The corresponding times for infants are not known, but the onset time for propofol in children (3-11 years of age) is 132 s [58]. It is therefore likely that the intubation conditions would have been better in both groups if we had waited longer after the injections.

In three studies with older infants and children [66, 68, 69], larger doses of remifentanil (3–4 μg/kg) added to propofol (3–4 mg/kg) resulted in excellent intubation conditions in nearly all of the patients; however, Blair et al. [67] could not achieve intubation with the first attempt in four of 27 children (3–12 years of age) receiving such doses and encountered at least one child who had closed vocal cords (Fig. 4 in [67]). In the present study, the cords were closed in a number of infants in the placebo group (Table 4). This finding could be due to an insufficient propofol or remifentanil dosage but could also be a problem specific to this age group. In fact, it is still not known whether or not the intubation of young infants can be consistently performed without relaxants or inhalational agents unless topical anaesthesia is applied.

Given these results, we now think it would have been worthwhile to have studied slightly higher doses of rocuronium than the 0.2 mg/kg used in the present study; however, that would also have prolonged the time for neuromuscular recovery, which was already non-negligible with the abovementioned dose. Thus, the time from injection until the Tw4/Tw1 ratio had reached 0.9 was 23 min. Even though the number of patients was small in our time-course study, it seems necessary with proper neuromuscular monitoring and adequate reversal at the end of anaesthesia, even after a low dose of rocuronium in infants.

It would also have been interesting to titrate the dose of remifentanil, but from an open trial, we were convinced that 2 μg/kg would be sufficient. Crawford et al. [68] determined the $ED_{98}$ value to 2.88 ± 0.5 μg/kg for acceptable intubations by using logistic regression analysis in infants. Hume-Smith et al. [111] found the $ED_{95}$ value for remifentanil to be as high as 5.0 μg/kg for infants 0–3 months of age together with propofol 5 mg/kg. These doses probably necessitate use of glycopyrrolate to avoid significant bradycardia.

# Study III

The main finding of this study involving 518 propofol anaesthetics in 401 individuals sensitised to peanuts and soy was that there were no incidents of allergic reactions.

In the first reports of allergic reactions to propofol there was no mention of a connection to food allergies [37-43]. Instead, it was believed that the reactions were IgE-mediated with the isopropyl and phenol groups of the propofol molecule acting as the epitopes [37, 38]. Later, it was suggested that because the drug emulsion contains egg lecithin and soy oil, propofol may be unsafe to use in patients allergic to egg, soy and peanuts. This has caused a reluctance amongst anaesthesiologists to use propofol in food-allergic patients, despite that guideline advice not to avoid propofol in these patients [82]. Also, product leaflets frequently list food allergies as contraindications to propofol use.

Our finding that propofol is safe to use in patients sensitised to peanuts and soy is consistent with previous studies that have investigated propofol in food-allergic patients [53, 81-83]. All of the studies concluded that propofol is safe to use, but the investigated food allergens and patient cohorts differed between the studies (Table 11). The explanation for the apparent absence of hyperreactivity in food-allergic patients is believed to be that refined egg lecithin and soy oil do not contain a sufficient amount of the allergenic proteins to trigger an allergic reaction [50, 51].

The relative strengths of the current study are the inclusion of both paediatric and adult patients, the number of patients and anaesthetics, the use of a control group and the defined time interval between diagnosis of sensitisation and anaesthesia.

The use of a control group enabled us to assess surrogate signs of allergy causing instability such as the frequency of administered anti-allergic drugs, circulatory support drugs and colloid fluids (Table 6). We found no differences between the groups in this regard. The vast majority of the anti-allergic drug class consisted of steroids in both groups. It is reasonable to believe that steroids were given more often as an anti-emetic than as an anti-allergic drug.

There was a higher incidence of reported soy and peanut allergies in the control group, suggesting a tendency to avoid propofol when allergy was reported prior to anaesthesia (Table 7). Indeed, avoiding propofol in these patients is consistent with the manufacturers' recommendations in Sweden. The tendency to avoid propofol in food-allergic patients has also been reported in other studies [54, 83]. It is acknowledged that this tendency may have introduced a selection bias in previous and present studies.

All patients in the study were diagnosed with sensitisation within 1 year of the anaesthesia. This minimised the possibility that the patients did not exhibit specific

IgE antibodies against peanuts and soy at the time of anaesthesia. Allergic sensitisation, however, does not equate to clinical allergy. Allergologic follow-up typically includes a clinical history and ideally, food provocation [112]. Because it was not possible to clinically evaluate the allergic status of the patients, self-reported allergies against peanuts and soy prior to anaesthesia were included in the study as a complement to allergic sensitisation.

The retrospective design of the current study is a limitation; however, given the apparent low incidence of allergic reactions to propofol in sensitised patients, it is doubtful whether a prospective study, designed and powered to detect differences in relevant outcome measures, ever will be undertaken.

**Table 11.**
A summary of studies on propofol use and food allergy to date.

| **Author** | **Murphy et al [53]** | **Molina-Infante et al [81]** | **Wiskin et al [82]** | **Asserhøj et al [54]** | **Mehta et al [83]** | **Gelberg et al** |
|---|---|---|---|---|---|---|
| Age group | Children | Adults | Children | Adults | Children | All |
| Food | Egg | Egg, soy, peanut | Egg, soy, nut | Egg, soy, peanut | Egg, soy | Soy, peanut |
| Allergy test | SPT, IgE | SPT, IgE | Not reported | IgE | Not reported | IgE |
| Source of clinical allergy | Medical record | Medical record | Medical record | Questionnaire | Medical record | Anaesthetic chart |
| Time between test and anaesthesia | Within 12 months | Not defined | N/A | Not defined | N/A | Within 12 months |
| Anaesthesias – no. | 43 | 404 | 149 | 171 | 65 | 518 |
| Patients – no. | 28 | 60 | 131 | 99 | <65 | 401 |
| Control group | No | No | No | No | Yes | Yes |

SPT = skin prick test; IgE = Immunoglobulin E; no. = numbers

# Study IV

The main finding of the present study was that rocuronium at a dose of 0.08 mg/kg reduced the handgrip strength at 60 s to approximately one-third compared to placebo, whereas the effect was minimally discernible after 0.04 mg/kg of rocuronium. The dose-dependent effect of rocuronium at these doses enabled the calculation of the effect corresponding to a therapeutic dose given for anaesthetic purposes. Thus, 0.2 mg/kg of rocuronium (67 % of the $ED_{95}$) was predicted to decrease the baseline handgrip strength to approximately 1 % at 60 s.

The $ED_{95}$ of a NMBA denotes the dose required to reduce twitch height by 95 %, which corresponds to 0.3 mg/kg for rocuronium [23]. While the standard intubating dose is 0.6 mg/kg, lower doses (0.1-0.3 mg/kg) have been suggested to avoid the inherent long recovery time for 0.6 mg/kg of rocuronium [29, 84, 113, 114]. We chose to predict the effect of 0.2 mg/kg of rocuronium because the recovery time to TOF $\geq$0.8 at a dose of 0.22 mg/kg in children 2-7 years has been found to be 16-24 min [113, 114], which should be acceptable, even for a short surgical procedure. Due to individual variability of sensitivity to NMBAs, it is difficult to foresee what NMBA doses are safe and at the same time produce measurable effects. Previous studies on awake subjects have shown variable effects of different NMBAs on various parameters at 13-35 % of the $ED_{95}$ [115-118]. Therefore, rocuronium doses at 13 and 27 % of the $ED_{95}$ were used in this study.

The reduction in maximum grip strength after a NMBA has previously been studied. Isono et al. [119] reported a 12 % reduction after 0.02 mg of pancuronium (29 % of the $ED_{95}$) and Kopman et al. [120] reported a 43 % mean reduction after mivacurium titration to TOF = 0.7; however, the effect on sustained handgrip strength of a NMBA measured with an electronic dynamometer has not been studied.

The finding that subparalyzing doses of rocuronium reduced the ability to maintain muscle force in the hand may explain how a low NMBA dose can facilitate intubation by reducing the ability to maintain the adduction force of the larynx. However, for several reasons it is difficult to generalize muscular effects in the hand to laryngeal muscles. In general, the neuromuscular blockade at the laryngeal muscles is less intense and with a more rapid onset and offset compared to the adductor pollicis muscle [24, 25]. This finding means that to achieve the same effect on the laryngeal muscles as in the hand, a larger dose must be given. These results do not necessarily apply to muscle endurance. Laryngeal muscles may be exquisitely susceptible to the fatigability effect of a NMBA considering that the intrinsic muscles of the larynx consist mostly of fast-twitch type II fibres in contrast

to the adductor pollicis muscle [121] and type II fibres show less endurance to work. Certainly, this reasoning needs to be corroborated in other studies.

While the effect of 0.08 mg/kg of rocuronium (27 % of the $ED_{95}$) on sustained muscle force was apparent, no effect on muscle function, as measured by twitch height of the thumb, was detected. Previous studies on twitch height by ulnar nerve stimulation after subparalyzing doses of a NMBA have shown some effect. Aziz et al. [115] found a decrease in the mean TOF ratio to 0.89 after 0.06 mg/kg of rocuronium (20 % of the $ED_{95}$) and Howardy-Hansen et al. [118] demonstrated a decrease in the median TOF ratio from 0.96 to 0.89 after 0.015 mg/kg of pancuronium (21 % of the $ED_{95}$). Although these results suggest TOF measurements to be a more sensitive method, a 0.1 Hz ST measurement was chosen because during the onset of NMBAs, which represents the time phase of the intubation manoeuvre, the decrease in twitch height is faster than the development of fade in TOF measurements [122-126].

A frequency of 0.1 Hz and a stabilization period of five minutes before drug injection were applied to avoid the gradual decrease seen in evoked response with frequencies ≥0.15 Hz [127] and a drift in twitch height, which is described during the first two to three minutes after calibration [128].

Perhaps the most plausible explanation for the lack of effect on single twitch height was the use of relatively low median currents (22.5 and 23.5 mA) in each group. Although TOF monitoring has been shown to be stable in the range of 20-30 mA in previous studies, amperage was recommended to be set 10-25 mA above threshold current [129-132]. Despite this uncertainty, it was important to keep the current as low as possible because of reported discomfort at current intensities of approximately 50 mA and sometimes even at lower currents [129, 133, 134].

Three subjects, including one subject in the placebo group, never returned to >90 % of the baseline twitch height. This fact, in addition to the absence of any significant NMBA effect, implies that the single twitch model used in the present study needs refinement.

The strengths of this study include the randomized double-blinded design; however, there were also several limitations. The low number of subjects increased the uncertainty of the results, especially the calculated data. In addition, the small size of the study means that the study may have been underpowered to detect differences in twitch height between groups. Furthermore, the study population may not be representative of sick, old and very young patient groups.

In conclusion, sustained handgrip strength is a more sensitive method of measuring low degrees of muscular blockade than a ST height. The findings suggest that low doses of rocuronium exert an effect partly by reducing muscular endurance in addition to a reduction in maximal strength.

# Conclusions

## Study I

The key findings of the present study were that remifentanil 0.5 µg/kg produced similar maximum depression of ventilatory drive as 1 µg/kg of fentanyl. The rapid effect on ventilation has to be considered when administering bolus doses of remifentanil to a spontaneously breathing patient.

## Study II

In conclusion, 0.2 mg/kg of rocuronium neither satisfactorily nor significantly improved intubation conditions above the conditions achieved with 3 mg/kg of propofol and 2 µg/kg of remifentanil. It is still not clear if intubation in infants can be achieved without a NMBA and without causing any harm to the vocal folds. Moreover, recovery data after neuromuscular blockade in infants with low-dose rocuronium needs further investigation.

## Study III

Our study on propofol administered to patients sensitized to peanuts and/or soy did not provide any data suggesting that it is unsafe to use propofol in this population. This adds to a slowly growing body of evidence to support the use of propofol in food-allergic patients. Despite the mainly unsubstantiated product leaflet warnings, it is reasonable to believe that propofol anaesthesia is safer than to choose less suitable alternatives on the basis of food allergies.

## Study IV

Sustained handgrip strength is a more sensitive method of measuring low degrees of muscular blockade than ST height. The findings suggest that low doses of rocuronium may exert an effect partly by reducing muscle endurance.

# Populärvetenskaplig sammanfattning

En narkos baseras i många fall på en kombination av olika läkemedel som tillförs via blodbanan där varje drog har olika effekt. Ett läkemedel ges för att inducera sömn, ett annat är smärtstillande och ett tredje ges för att åstadkomma en muskelrelaxation som framför allt behövs för att placera en plasttub i luftstrupen (intubation) för att säkra ventilationen av patienten under narkosen. Ibland är också muskelavslappningen nödvändig för det kirurgiska ingreppet. När nya läkemedel kommer i bruk har detta föregåtts av många och långa tester på både friska försökspersoner och på patienter där bl a preparatets effekter på individen (farmakodynamik) och hur individen omsätter preparatet (farmakokinetik) noggrant har utvärderats.

Denna avhandling baseras på fyra studier med olika frågeställningar kring tre narkosläkemedels funktioner.

Remifentanil är ett kraftigt smärtstillande morfinliknande preparat. Effekten är extremt kortvarig och det behöver därför vanligtvis ges som en kontinuerlig tillförsel. Den största fördelen är att behandlingen är extremt styrbar och att effekten snabbt försvinner när tillförseln stoppas. Nackdelen är att man behöver planera för annan smärtstillande behandling efter ingreppet om detta är förknippat med kvarvarande smärta. Det finns dock tillfällen där patienter utsätts för smärtsamma men kortvariga procedurer som inte är förknippat med någon kvarvarande smärta.

Den smärtstillande effekten av remifentanil jämfört med andra liknande läkemedel har tidigare studerats men samtliga morfinliknande läkemedel har även andra effekter, som att exempelvis dämpa andningsfunktionen. Den effekten är inte lika väl undersökt. I artikel I studerade vi den andningsdämpande effekten av tre olika doser remifentanil och jämförde med en ”standarddos” fentanyl på frivilliga försökspersoner. Fentanyl är ett annat vanligt förekommande morfinliknande preparat men med längre effekt. För smärtstillande effekt är samma dos remifentanil och fentanyl jämförbara men resultatet av studien visar att remifentanil är dubbelt så potent som fentanyl när man tittar på den andningsdämpande effekten.

Nackdelen med att ge en full dos muskelrelaxerande läkemedel är att man vid ett kortvarigt ingrepp fortfarande kan ha en kvarvarande effekt vid operationens slut. Detta kan då påverka patientens förmåga att andas. Det är visat att man kan intubera utan att ge muskelrelaxerande läkemedel men då behöver man kombinera tämligen

höga doser av narkosmedel och smärtstillande läkemedel vilket kan ge ogynnsamma effekter på puls och blodtryck, framför allt hos de minsta barnen, äldre patienter och personer med hjärt-kärlsjukdomar.

I artikel II testade vi hypotesen att ett tillägg av en låg dos muskelrelaxerande läkemedel (rocuronium) i kombination med måttliga doser propofol och remifentanil skulle ge bättre intubationsförhållande på 70 spädbarn jämfört med om rocuronium utelämnades. Vi fann ingen signifikant skillnad i förhållanden vid intubationen mellan grupperna.

Propofol är det vanligaste förekommande läkemedlet för att inducera sömn vid narkos. Det har en gynnsam profil med få biverkningar vilket gör det till ett mycket användbart narkosmedel i många situationer. Propofol är löst i bl a sojaolja. I Sverige och i många andra länder anges därför allergi mot soja och jordnöt (pga risk för korsreaktion med sojabönor) som en kontraindikation till att använda propofol. Dock finns det bara sporadiska, anekdotiska fallbeskrivningar som skulle kunna styrka detta samband.

Artikel III är en retrospektiv registerstudie där vi samkörde patienter med känd allergi mot soja och/eller jordnöt med data från operationsplaneringssystem. Vi fann 544 personer som genomgått 725 narkoser. 518 av dessa narkoser genomfördes med propofol och vid 207 tillfällen användes ett annat narkosläkemedel. Tre fall bland dem som sövdes med propofol och två fall i gruppen som sövdes med ett annat läkemedel uppfyllde kriterier för allvarlig allergisk reaktion. Ett av fallen i propfolgruppen behövde akut behandling som vid misstänkt allergi. Senare uppföljning kunde dock inte bekräfta någon allergi och patienten kunde vid ett annat tillfälle, utan problem, sövas med propofol. Inget av de andra fallen följdes upp men vid granskning av journalerna gjordes bedömningen att organpåverkan troligtvis inte berodde på propofol eftersom ingen behandling mot allergisk reaktion gavs och att symtomen snarare orsakades av en övergående blodtryckssänkning som ibland ses efter givet narkosläkemedel.

När man ger ett muskelrelaxerande läkemedel påverkas signalsystemet mellan nervändan och muskeln och muskelkontraktionen påverkas. Hur uttalad muskelrelaxationen blir beror på hur många nerv/muskelenheter som påverkas som i sin tur avgörs av hur stor dos läkemedel som givits. Syftet med muskelrelaxation i samband med intubation är att relaxera muskulaturen kring stämbandsplanet för att lättare kunna föra ner en plasttub förbi öppna stämband.

Det finns sedan tidigare omfattande dokumentation kring den muskelavslappande effekten av olika doser muskelrelaxantia och dess påverkan på skilda muskelgrupper. Det finns också studier som visar att redan vid tillförsel av en liten dos muskelrelaxantia skulle man kunna få lika bra intubationsförhållanden som vid en större dos. Effekten av denna låga dos kan inte enbart förklaras av en

muskelparalys. I artikel IV testade vi hypotesen att effekten av en låg dos muskelrelaxerande läkemedel (rocuronium) även skulle kunna förklaras av en ökad uttröttbarhet i muskulaturen. Friska försökspersoner fick vid tre olika tillfällen två extremt låga doser rocuronium samt koksalt (placebo) samtidigt som statisk muskelkraft över tid mättes med en handdynamometer. Det blev en knappt märkbar skillnad mellan den lägsta dosen och koksalt. Efter den något högre dosen (som fortfarande var extremt låg) minskade däremot uthålligheten påtagligt och var endast en tredjedel jämfört med placebo vid samma tidpunkt. Trots denna påtagliga skillnad i uthållighet kunde vi inte notera någon grad av muskelparalys med konventionell övervakningsmetod.

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# Aspects of intravenous anaesthesia

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