The Effect of Titrated Fentanyl on Cough Response in Healthy Participants

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A thesis submitted in partial fulfillment of the requirements for the

Degree of Master of Science in Speech and Language Sciences

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Abstract

Background: One population prone to aspiration pneumonia and impaired cough is the postoperative patient. Postoperative pneumonia is the third most common complication among surgical patients after urinary tract and wound infections (Wren, Martin, Yoon, & Bech, 2010). A patient who has their surgical course complicated by aspiration pneumonia has increased morbidity, increased length of hospital stay and places greater demands on the health system. Mortality rates are cited as high as 70% (Wren, et al., 2010). Despite the prevalence of postoperative pneumonia and the high morbidity and mortality rates, little is known about the effect of anaesthesia on swallowing and airway protection. This study investigated the effect of clinical doses of fentanyl on suppressed cough reflex in healthy participants.

Materials and Methods: After receiving ethical approval, 14 young, healthy participants gave informed written consent and completed the study protocol. Each participant received a total of 2 mcg/kg of fentanyl in four doses administered at five-minute intervals. Fentanyl effect site concentrations (ESC) were estimated using a standard pharmacokinetic model. During the administration period, suppressed cough response testing (SCR) with nebulised citric acid was performed after each fentanyl dose. Citric acid was presented in increments of 0.2M from each participant's baseline cough response until a present-strong response was achieved. During the post-administration period, SCR was compared with reducing effect site concentrations to determine the time course for resolution of cough suppression.

Results: Suppressed cough threshold increased and decreased in parallel with modeled fentanyl effect site concentrations. Mean citric acid concentration increased from 0.5M at baseline to 0.6M after 0.5 mcg/kg of fentanyl, 0.7 M after 1 mcg/kg of fentanyl, 0.9M after 1.5 mcg/kg of fentanyl and 1.2M after 2 mcg/kg of fentanyl. Predicted effect site

concentrations after final doses of fentanyl (2 mcg/kg) were 1.89 ng/mL (1.81-1.96), well within the range seen clinically in the postoperative period. After the final dose of fentanyl, participants had on average 3.4 increments of change in their cough response (at increments of 0.2M).

Conclusion: SCR testing with citric acid is sensitive enough to mirror changes in fentanyl ESC in healthy, young participants. The degree of reflex suppression seen has been associated with an 8-fold increase in aspiration risk in the general medical patients with dysphagia (Miles, Moore, McFarlane, Lee, Allen, Huckabee, 2013). Further research into the application of SCR in the postoperative period may help clinical decisions regarding safety to commence oral intake.

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Preface

This MSc (Speech and Language Sciences) thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (6th edition) and spelling recommended by Oxford Dictionary (http:oxforddictionaries.com/).

The research for this thesis was carried out between January and May 2013 while the student was enrolled in the Department of Communication Disorders, University of Canterbury. Research was conducted at Christchurch Hospital and was supervised by Dr Maggie-Lee Huckabee and Dr Geoffrey Shaw.

List of Abbreviations

Abbreviation	Definition
0_2	Oxygen
CNS	Central nervous system
CR	Cough reflex
CRT	Cough reflex test
EMG	Electromagnetic surface myography
ER	Expiratory reflex
ERS	European Respiratory Society
fMRI	Functional magnetic resonance imaging
IV	Intravenous
LER	Laryngeal expiratory reflex
MAOI	Monoamineoxidase inhibitor
mg	Milligram
NA	Nucleus ambiguous
NTS	Nucleus tractus solitarius
pH	Phosphorous
PNS	Peripheral nervous system
RAR	Rapidly adapting stretch receptor
RCT	Reflex cough test
RLN	Recurrent laryngeal nerve
SAR	Slowly adapting stretch receptor
SCR	Suppressed cough response
SLN	Superior laryngeal nerve
δ	Delta opioid receptor
κ	Kappa opioid receptor
μ	Mu opioid receptor
μg	Microgram

Chapter 1: Literature Review

Dysphagia

Dysphagia is the medical term for difficulty with swallowing (SPAA, 2012). It is recognised in the International Classification of Functioning and Health by the World Health Organization (www.who/int/classifications/icf/en). International dysphagia prevalence data within the acute hospital setting vary dramatically. Australian figures have been reported at 25% (Cichero, Heaton, & Bassett, 2009) with Spanish figures as high as 55% (Cabre, Serra-Prat, Palomera, Almirall, Pallares & Clave, 2010). One American study reported rates of less than 1% of hospital admissions related to dysphagia (Altman, Yu, & Schaefer, 2010), although they recognise this is likely grossly underreported. Caution should be used in directly comparing international rates of dysphagia, given the varying methods used by the investigators. For example, in comparing the studies of Cichero et al. (2009) and Cabre at al. (2010), the nature of the samples are very different: 442 Australian patients of unspecified age from general medical wards with various reasons for admission, versus 134 Spanish patients aged over 70 (mean age 84.51) in an acute geriatric unit who were admitted with pneumonia, respectively. It may be these methodological and sampling differences explain the discrepancy between the results, rather than country of data collection alone.

The consequences of dysphagia in the hospitalised patient can be vast. There are social and psychological effects as well as risk of nutritional compromise (Ekberg, Hamdy, Woisard, Wuttge,ÄìHannig, & Ortega, 2002). Dysphagia increases length of stay and is a poor prognostic indicator (Altman, Yu & Schafer, 2010). In an analysis of the 2005-2006 American National Hospital Discharge Survey data, Altman et al., (2010) found the median length of stay was 4.04 days for patients with dysphagia, versus 2.40 days for those without.

Aspiration.

A primary complication of dysphagia which must be managed in the acute setting is aspiration (Wilkins, Gillies, Thomas, & Wagner, 2007). Aspiration, especially if it goes undiagnosed, is often the determining factor which increases patient mortality (Altman, et al., 2010). Aspiration occurs when material enters the larynx and passes below the level of the vocal folds. It may be signaled with a cough response (overt aspiration) or may occur in the absence of a cough response (silent aspiration). Silent aspiration poses a number of difficulties in patient management, primarily because it is poorly detected at bedside (Ramsey, Smithard, & Kalra, 2005).

Historically, the terms 'aspiration', 'aspiration pneumonia' and 'aspiration pneumonitis' have been poorly defined in the literature (Finucane & Bynum, 1996). Aspiration of colonised oropharyngeal material results in aspiration pneumonia; defined as an acute pulmonary inflammation response to bacteria. Aspiration of sterile gastric contents results in aspiration pneumonitis; an acute lung injury similar to that of a burn in response to acidic gastric material (Marik, 2001). The scientific distinction between these two processes can be made based on bacteria type, acidity of material etc. For example: a pH lower than 2.5 and a volume of at least 20mL are required for the development of aspiration pneumonitis (Marik, 2001). However in clinical terms, aspiration (regardless of type of material) occurs due to a breakdown in airway protection reflexes at the level of the vocal folds.

One of the most widely cited articles pertaining to aspiration in the medical speech pathology literature is that of Langmore, Turpenning, Schork, Chen, Murray & Lopatin et al., (1998). In her landmark study, Langmore followed 189 patients over four years to identify the most important risk factors for developing aspiration pneumonia. She offered a three-period process to explain the multifactorial development (see figure 1). Firstly, bacteria are colonised in the oropharynx, secondly, the bacteria are conveyed into the lungs through

aspiration and lastly, impaired pulmonary clearance is ineffective at clearing the aspirated material.

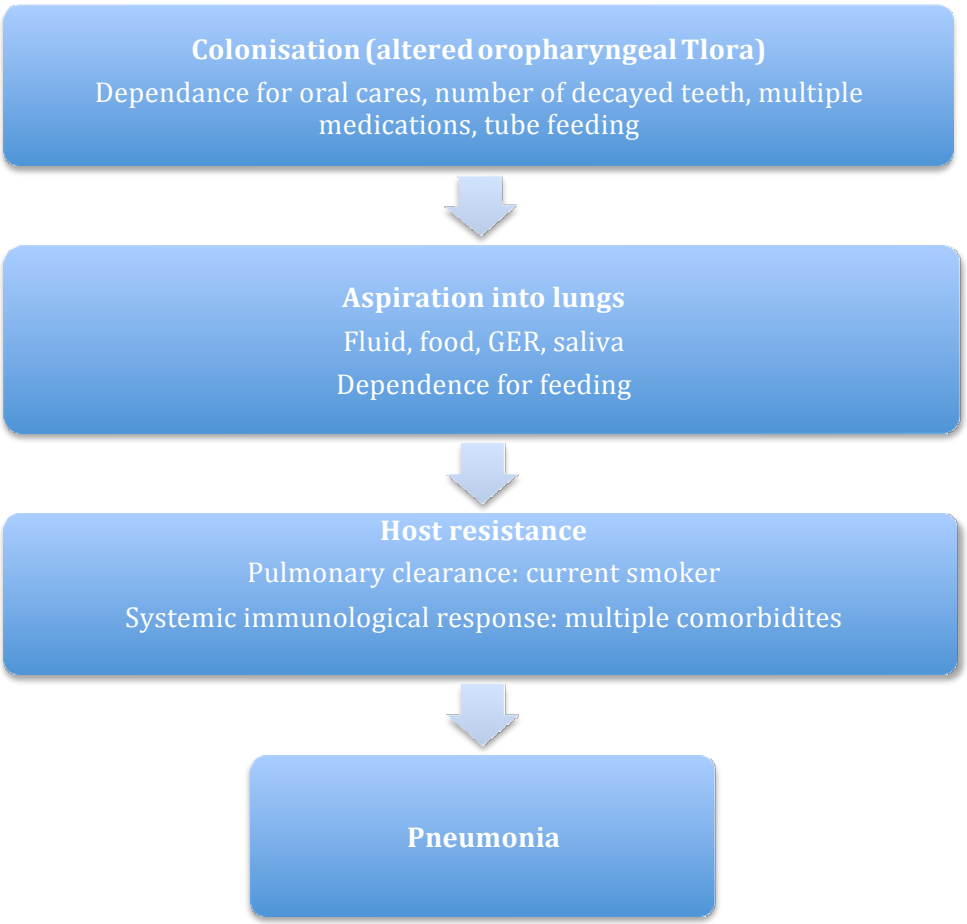

Figure 1. Three-phase process for developing aspiration pneumonia modified from Langmore et al., (1998) p.77.

Healthy individuals aspirate small amounts of their own saliva (Langmore, et al., 1998), and approximately 50% of healthy people microaspirate secretions during sleep (Gleeson, Eggli, & Maxwell, 1997). However, not everyone who aspirates develops pneumonia. The above model helps explain why. All three conditions: colonisation, aspiration and impaired resistance must be met. While a small amount of aspiration in healthy, mobile individuals is normal, aspiration can be fatal for patients with altered oropharyngeal flora due to reliance on others for oral cares or tube feeding, those with

dysphagia putting them at increased risk of aspiration, or those with compromised resistance because of decreased mobility and multiple medications.

There are limitations of the Langmore et al. (1998) study. Subjects were all male veterans aged 60+ years and 112 of the 160 participants had multiple co-morbidities. Also, all patients received treatment. However, it was prospective in nature, included a follow up period of four years and had a large number of participants and a control group. The definition and distinction of aspiration according to three medical criteria was clearly documented and reached by consensus of an experienced panel. Their procedures were detailed and each participant received a number of radiographic/ nuclear medicine assessments of pharyngeal and oesophageal swallowing function. The overall results of Langmore's study included a larger number of variables and categories of risk than had previously been investigated. Despite being published fifteen years ago, it is still regarded as one of the most important papers on this topic. Langmore's three phase process verified clinical knowledge - in order for bacteria to enter the lungs, it must be aspirated and bypass the typical mechanisms of airway protection.

Airway Protection

Aspiration occurs when there is a breakdown of airway protection mechanisms. Airway protection reflexes are: swallowing aponea, cough, expiratory effort and laryngeal closure (Widdicombe, 1998). The primary mechanism for airway clearance in humans is the cough. Cough is designed to protect the airways from foreign matter once airway closure has been ineffective (Pantaleo, Bongianni, & Mutolo, 2002; Dua, Surapaneni, Kuribayashi, Hafeezullah, & Shaker, 2011; Lee & Birring, 2012) and is a critical mechanism in airway defense (Fontana & Lavorini, 2006; Addington, Stephens, Phelipa, Widdicombe, & Ockey, 2008). The definition of cough currently accepted by the European Respiratory Society

(ERS) was initially published by Korpas & Tomori (1979). They classify cough as a three phase motor act characterised by an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) with subsequent opening of the glottis and rapid expiratory airflow (explusive phase).

Airway protection is so essential to human survival that the normally developing human fetus can swallow in the 12th week of gestation, prior to development of cortical and subcortical structures (Jean, 2001). With maturation, different features of airway protection emerge. When water is presented into the pharynx of premature infants they respond with multiple swallows, aponea and stridor. Full term infants have the same type of responses but of decreased duration. Mature infants respond with a brief aponea and then multiple swallows (Thach, 2007). As children mature, aponea and swallowing become less common and the cough reflex becomes the primary feature of laryngeal protection in man (Thach, 2007).

Cough neurophysiology.

It is generally accepted that the cough reflex is triggered by an irritant stimulating vagally innervated sensory receptors within the respiratory tract (Dicpinigaitis, 2003). The entire respiratory tract is densely packed with sensory nerve endings. The larynx, the trachea and major bronchi are the areas with greatest density of receptors (Fujimura, 1995). The literature discusses a number of receptor types, categorised according to origin, location, neurochemistry and responsiveness: chemoreceptors, C fibres, nocioceptors, mechanoreceptors (including rapidly and slowly adapting stretch receptors), sodium ATPase receptors and general ‘cough receptors’ (Mazzone, 2005).The larynx has two types of cough receptors: myelinated irregularly firing receptors (Poliacek, Halasova, Jakus, Murin, Barani & Stransky et al., (2007) and nonmyelinated C fibre endings (Fujimura, 1995). These are both innervated by the superior laryngeal nerve of vagus (Widdicombe, 1998). The tracheobronchial tree also has two types of cough receptors: myelinated rapidly adapting receptors (RARs) also

called mechanoreceptors, and nonmyelinated bronchial C fibre endings. These are both innervated by the pulmonary branch of the vagus (Widdicombe, 1998). These sensory receptors relay afferent information through action potentials to the nucleus tractus solitarus, where it synapses in the putative 'cough centre' in the dorsal medulla of the brainstem (O'Connell, 2002). This initiates coordinated motor output: the cough (Nasra & Belvisi, 2009).

Cough reflex versus expiratory reflex.

The general term 'cough' can further be defined into different processes which have the same observable outcome: the cough reflex and the expiratory reflex. The classic cough reflex (CR) has three phases: an inspiratory phase, a compressive phase and an expulsive phase (Korpas & Tomori, 1979) as described above. The purpose of the inspiratory phase is to increase the force of the explusive phase to support clearance of the tracheobronchial tree and lungs. The CR is triggered by receptors within the tracheobronical tree (Fontana & Lavorini, 2006).

The expiratory reflex (ER) also known as the laryngeal expiratory reflex (LER) (Fontana & Lavorini, 2006; Widdicombe & Fontana, 2006) has only two phases: a strong expiratory phase (against a closed glottis) and an open expiratory phase (as the glottis opens) to eject material from the larynx (Tatar, Hanacek, & Widdicombe, 2008). Notably, it does not begin with an inspiratory phase; this could permit entry of material into the lungs. The ER is triggered at the level of the true vocal folds or upper trachea (Fontana & Lavorini, 2006).

The CR and the ER have distinctive afferent pathways, CNS circuits, physiological presentations and effects to medication (Fontana, 2008). The CR tends to be associated with an 'urge to cough' while the ER does not (Davenport, Vovk, Duke, Bolser, & Robertson, 2009). The CR is initiated in the cortex, is triggered by mechanical or chemical stimuli and can be cortically modulated and suppressed. The ER is initiated by the brainstem and can not

be cortically modulated or suppressed (Miles, Zeng, McLauchlan, & Huckabee, 2013). Clinically, it is likely a combination of the CR and the ER that protect the airway in a cough epoch (Fontana, 2008; Miles, Zeng, et al., 2013). However, an understanding of the differences and commonalities across the two reflexes is an essential part of research design in this field.

Cortical influence on cough

The cough reflex is more susceptible to cortical modulation and suppression than the ER. A further distinction is required between types of cough reflex. Humans are capable of both volitional and reflexive cough, the difference being the involvement of the cortex, which implies different and distinct pathways (Lee, Cotterill-Jones., & Eccles, 2002). Voluntary cough can not be studied in animals (Lasserson et al., 2006) and some researchers have questioned whether the reflexive cough elicited in anaesthetised animals can be applied directly to man (Nasra & Belvisi, 2009; Lasserson, et al., 2006). The supramedullary activation of cough under these conditions is even more doubtful (Widdicombe, Eccles, & Fontana, 2006). Volitional cough in humans is often associated with urge to cough, which implies cortical involvement. Despite not understanding the exact mechanisms, we know that cough can be affected by cortical input. Figure 2 represents volitional and reflexive cough pathways.

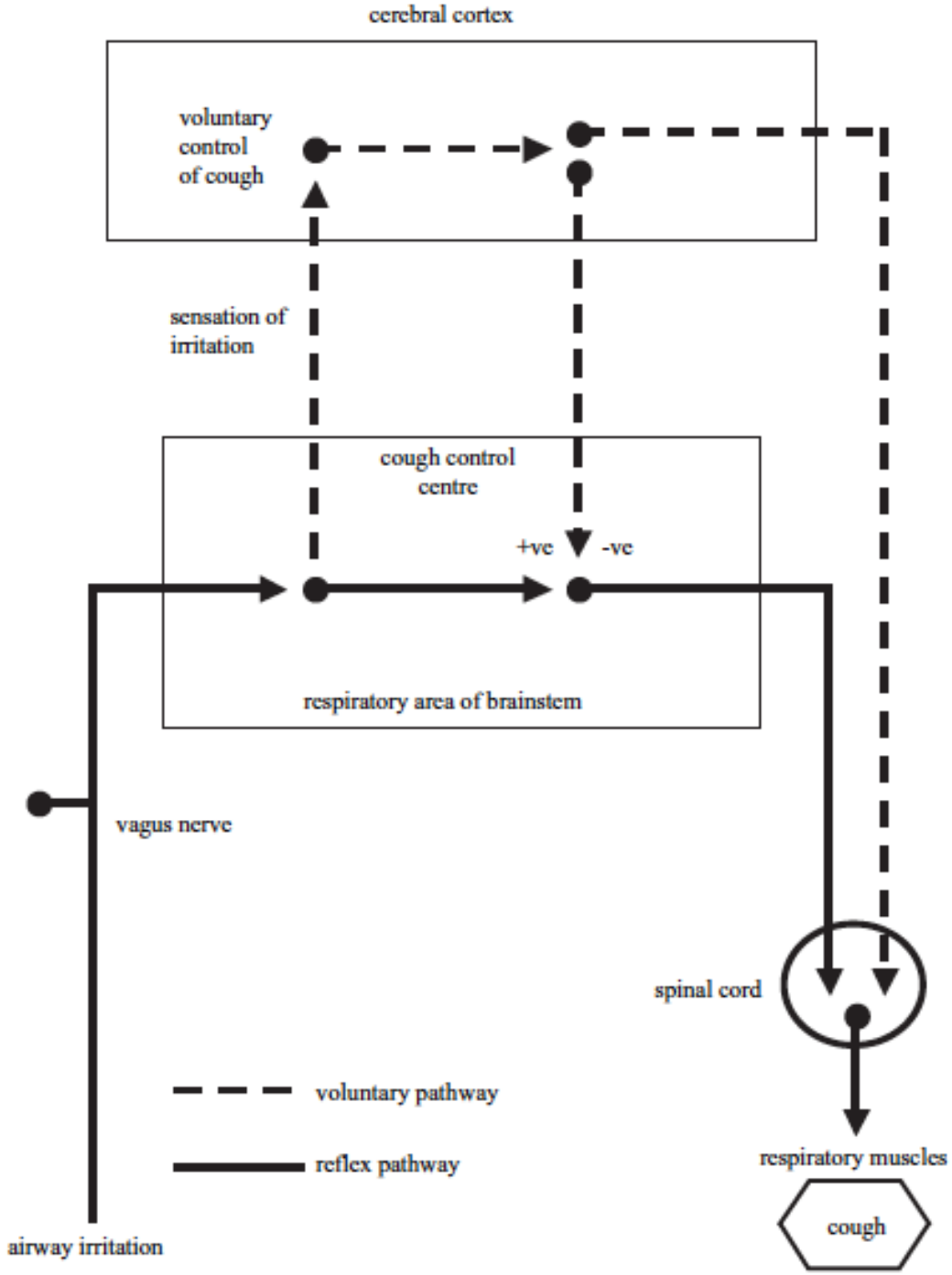

Figure 2. Representation of volitional and reflexive cough pathways (Lee, et al., 2002, p319).

Lasserson et al., (2006) compared cough flow rates and EMG measurements of abdominal muscles in volitional versus reflexive cough elicited with tartaric acid. They found the maximum cough flow rate was higher in volitional compared to reflexive cough, and that

volitional cough initially activated expiratory muscles and recruited shoulder and thoracic accessory muscles as cough strength increased, while in reflexive cough EMG onset was simultaneous for both expiratory and accessory muscles. They reported the variances in volitional versus reflexive cough were explained by functional organizational differences of muscle activation. Bolser & Davenport (2002) report that in voluntary cough, subjects can determine the perceived need for input of additional accessory muscles.

To highlight the influencing role of the cortex in cough, there is a body of research that shows higher suppressed cough thresholds compared to natural cough thresholds. In suppressed cough testing, participants are instructed to try not to cough. The first to investigate this phenomenon were Hutchings, Morris, Eccles & Jawad (1993). They studied 24 healthy young volunteers. In the natural condition, 23/24 coughed at their highest dose of capsaicin, compared to only 3/24 at the same dose in suppressed cough condition. Similar results have been found since. Significantly higher suppressed cough thresholds than natural cough thresholds to citric acid were observed in both healthy participants and those with Parkinson's disease, regardless of age or disease severity (Leow, Huckabee, & Anderson, 2006). Monroe (2010) studied 80 healthy participants (elders and youngers matched for gender). She found a statistically significant difference between natural and suppressed cough responses (mean= 0.86 and 1.39 respectively) in the younger group ($p=0.001$). Hegland, Bolser & Davenport (2012) investigated 20 healthy participants using very high concentrations of capsaicin. In the suppressed condition, they observed a number of airway protective behaviors other than cough (swallowing, throat clearing, breath holding). They concluded that healthy participants can modify their cough response by using these behaviours, even at high doses of capsaicin where suppression is not possible.

Further supporting the role of the cortex in cough modulation is the suppression of the reflexive cough during sleep (Lee & Birring, 2010; Hsu, 1994; Nishino, Tagaito, & Isono,

1996; Widdicombe & Singh, 2006). Wang, Nakagaawa, Sekizawa, Kamanaka, & Sasaki (1998) assessed 11 patients and 12 controls across a 24 hour period. They demonstrated significantly higher cough thresholds to citric acid at night compared to the day in both the patient group (with a history of aspiration pneumonia) and the control group. Interestingly, all 'night' coughs were associated with arousal.

Cough is also known to be suppressed during anaesthesia (Kluger & Short, 1999; AstraZeneca., 2012; LeGrand, Khawam, Walsh, & Rivera, 2003). Tagaito, Isono, & Niskino (1998) investigated the effects of combined propofol anesthesia and fentanyl on airway reflexes of 22 healthy female patients. They presented distilled water to the laryngeal mucosa and recorded responses as CR, ER, aponea or spasmodic panting. They clearly defined each term in their study and had robust verification procedures in place. They found of all the airway reflexes, the CR was the most susceptible to the opioid fentanyl. Several studies in man have shown that inhaled opiates do not suppress the CR (O'Connell, Thomas, Fuller, Pride, & Karlsson, 1994). However, inhaled opiates are not used clinically, limiting the application of this research to clinical practice. Of more interest is the finding that systemic opiates (intravenous administration) do suppress the CR (Fuller, Karlsson, Choudry, & Pride, 1988; O'Connell, 2002). A limitation of the Fuller et al., (1998) study was that participants who underwent the inhaled and oral administration of opioid were not the same participants who received the IV administration of opioid, making intra-subject assessment across conditions impossible.

O'Connell (2002) reported a significant effect of IV morphine on capsaicin cough response. This was significantly attenuated by pre-treatment with the serotonin inhibitor pizotifen, compared with saline. However, the authors did not use an effect site concentration model to more precisely determine the action of morphine at the time of cough testing. Patients received 0.15mg/kg of morphine administered over 15 minutes dependent on weight,

and the pre-treatment with piztofen was a set dose of 1.5mg, given at 12 hours and 2 hours pre-IV infusion of the opioid.

Cough reflex testing.

Given the importance of cough as the primary airway defense mechanism and the implications of impaired cough (morbidity and mortality) for the hospitalised patient, cough reflex testing (CRT) is now used in clinical speech pathology practice to assess the integrity of the laryngeal cough reflex (Fujimura, 1995). CRT is also known as the inhalation cough challenge (Dicpinigaitis, 2007; Morice, Kastelik, & Thompson, 2001) or reflex cough test (RCT) (Addington, Stephens, & Gilliland, 1999). It is distinct from bronchial provocation tests. Cough reflex testing involves the delivery of a tussive agent whereas bronchial provocation testing involve the delivery of constricting substances (Morice, et al., 2001).

Cough reflex testing began in the 1950's as a response to the expanding production of synthetic antitussive drugs and the need to test and compare efficacy (Bickerman, Barach, & Drimmer, 1954). Prior to this, antitussive effectiveness had been assessed using ammonia vapor, cigarette smoke or sulphur dioxide (Gravenstein, Devloo, & Beecher, 1954). These tests were unpleasant and often conducted on institutionalized patients (Cass & Frederik, 1951). There are a number of potential methodological flaws with trials using this patient group. They were presumably more likely to be on antipsychotic or sedative medications which could affect central nervous system function, they commonly had co-morbidities including respiratory disease and or chronic cough (Cass, 1951) and they tended to have a rather variable presentation (Bickerman, et al., 1954). All these factors make it difficult to apply any findings of an antitussive effect to the general population.

Bickerman et al., (1954) aimed to achieve three design features in their cough reflex test: 1) consistent intra-subject response to a set dose of citric acid; 2) reliability of that response across time and 3) an overall test which was non-toxic and simple to administer, to allow for large scale normative studies to be undertaken. Despite these design features being proposed over fifty years ago, unfortunately the literature still does not have a standard method of administration for the cough reflex test. The delivery of tussive agents in cough challenge requires a nebuliser to convert the liquid agent into aerosol particles (Morice, et al., 2001). The diameter of the particles affects where they will be deposited in the respiratory tract. Several nebulised chemical stimuli can induce cough in man and animals (Nasra & Belvisi, 2009). Bickerman et al., (1954) tested 33 different aerosol substances in 153 patients over a two year period. They overcame the flaws of prior studies that had investigated institutionalised patients only by testing healthy volunteers, who more likely represented the general population. They did, towards the end of recruitment, include 17 participants who had well-controlled asthma. The results indicated that citric acid, tartaric acid and benzoic acid yielded more consistent responses than the other 30 agents. These results were supported by recent literature indicating capsaicin and citric acid are the most reproducible agents (Morice, Fontana, et al., 2007).

The most widely used agents in cough testing today are citric acid, tartaric acid and capsaicin (Morice, et al., 2001). Citric acid and tartaric acid are organic acids (Bickerman, et al., 1954). Capsaicin is the active ingredient in red pepper (Fujimura, 1995). One benefit of citric acid is that if the chemical stimuli causes a mechanical distortion of the nerve terminal it can activate both chemoreceptors and low threshold mechanoreceptors (Mazzone, 2005). High doses of opiates inhibit capsaicin induced cough, while beta agonsist medications such as sodium cromoglycate and nedocromil sodium do not affect capsaicin (Fuller, 1991).

Perhaps the most discernible difference in cough testing between different research groups is the administration method: single dose or dose response method (see figure 3). Single dose inhalation challenge involves presentation of one set concentration of the tussive agent (Morice et al., 2007). This is a rapid method of assessment which has been used largely in screening studies and when investigating duration of anti-tussive agents such as menthol and dextromethorphan on cough reflex (Morice, Marshall, Higgins, & Grattan, 1994).

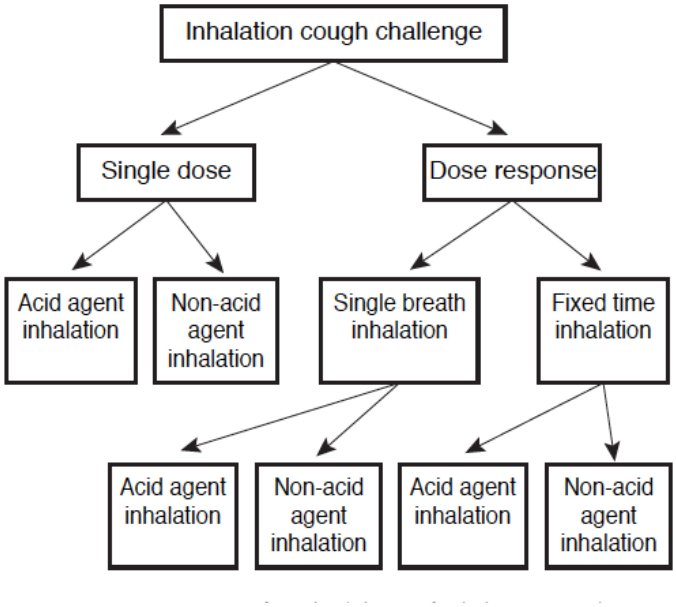

Figure 3. Different methodology used in cough testing (Morice, et al., 2001, p367).

Dose response challenge involves presentation of increasing concentrations of the tussive agent, with placebo presentations of saline. Dose response is also known as threshold testing. This method is further categorized into single breath and fixed time inhalation challenges. Single breath has subjects perform maximum exhalation and inhale via mouthpiece for 1 second. Fixed time inhalation usually ranges from 15- 60 seconds. However, the ERS guidelines state the sixty-second inhalation period has been conducted with a small number of subjects, has delivery complications and should no longer be used (Morice, Fontana, et al., 2007).

The dose of tussive agent required to elicit two successive coughs and/ or five successive coughs is reported, respectively known as C2 and C5 response. There is a debate as to which value has the most clinical importance, however researchers such as O'Connell, Thomas, Studham, Prode & Fuller (1996) report C2 is the more reproducible measure.

Tachyphylaxis is the diminished system response to latter increments of presentation of the tussive agent (medical-dictionary.thefreedictionary.com). It can occur in repeat cough challenges (Morice, et al., 2007). Compared with dose response testing, single dose method has a lower likelihood of inducing tachyphylaxis due to the smaller number of inhalations required. Tachyphylaxis is therefore a risk of the dose response approach. To prevent this, a period of between 30-60 seconds rest between administrations is recommended (Morice, 1996).

Due to the distinction between natural and suppressed cough conditions; consideration should be given to the instructions patients receive in the administration of cough testing. Typically, under the 'natural' condition, the instructions will be "cough if you need to" (or similar) which may alert the cognitively intact patient to the likelihood of coughing. In the suppressed condition, patients are typically instructed to "try not to cough" and this may in fact represent a better assessment of reflexive cough.

There is currently no gold standard for methodology of cough reflex testing administration, and due to difference in protocols and it is not possible to compare results between research groups (Barber, 2005; Morice, et al., 2001). However, there is a growing body of evidence that cough reflex testing gives useful clinical information. Nakajoh, Nakagawa, Sekizawa, Matsui, & Sasaki (2000) showed a significant inverse relationship between strength of cough reflex and incidence of pneumonia in the stroke population.

Clinical application of cough testing in swallowing assessment.

In clinical dysphagia management, it is often difficult to determine whether a patient's airway protection mechanisms are intact or not, affecting decisions such as when eating and drinking can safely be commenced (Addington, Stephens & Gilliand, 1999). We have long known that traditional bedside evaluations are insensitive to the phenomenon of silent aspiration. An important paper by Splaingard, Hutchins, Sulton, & Chaudhuri (1988) reported that up to 70% of silent aspirators went undiagnosed on bedside swallowing exam. In applying the findings of that paper to clinical practice, it is likely that these patients were started on oral diets and put at risk of aspiration pneumonia because it was not possible to differentiate silent aspirators from non-aspirators.

Addington et al., (1999) evaluated the use of cough testing for identifying acute stroke patients at risk of silent aspiration. Administration was via mouthpiece using a tartaric acid solution. Response was described as normal or abnormal. Of the 400 patients who had a normal response, only 5 went on to develop aspiration pneumonia (1.25%) compared to the control group of 204 patients, who received traditional assessment, in which 27 went on to develop pneumonia (13.25%). These results supported the clinical application of cough testing in identifying stroke patients who were at risk of silent aspiration. One limitation of the Addington et al. (1999) study was population bias. The treatment group was from one hospital, the control group from a 'sister' hospital. The treatment group was comprised only of patients who were able to follow the commands required to complete CRT via mouthpiece administration. Using a mouthpiece and requiring participants to fully exhale and then deeply inhale requires a degree of receptive language skill and motor control not always seen in the acute stroke population due to the high incidence of aphasia, cranial nerve impairment and apraxia. The control group included those with severe deficits who would have been excluded from the treatment group. This may have skewed the results.

More recently within New Zealand, researchers have implemented a facemask administration method which requires participants to breathe passively for 15 seconds using a nebuliser with a set output of 8L/minute and citric acid (Leow, et al., 2006; Miles & Huckabee, 2012; Miles, Moore, et al., 2013; Miles, Zeng, et al., 2013). Results of their cough sensitivity data correlate highly to instrumental investigations such as videofluoroscopy and fibreoptic endoscopic evaluation of swallowing. They found that at a dose of 0.8M citric acid, patients who had an abnormal cough response were 8 times more likely than those with a present response to silently aspirate under videofluoroscopy (odds ratio of 8.0) (Miles, Moore, et al., 2013).

The literature surrounding the application of cough reflex testing in dysphagia management is substantial; discussion of all of which is outside the scope of this review. Landmark studies with the greatest relevance to this research have been reviewed above.

Postoperative aspiration

One population prone to aspiration pneumonia with an etiology of impaired cough is the postoperative patient. Potential risk factors for aspiration include oesophageal disease (Kluger & Short, 1999), obesity (Kluger & Short, 1999), neurologic impairment (DeLegge, 2002), advancing age (DeLegge, 2002), gastroesophageal reflux (DeLegge, 2002), tube feeding (DeLegge, 2002) and decreased level of consciousness, including anaesthesia (DeLegge, 2002; Nishino & Hiraga, 1991).

Aspiration is a known risk of general anaesthesia, occurring in approximately 1 of 3000 operations (Marik, 2001). In a national survey, 71% of New Zealand based specialist anaesthetists reported between 1 and 10 instances of aspiration during their career (Kluger & Willemsen, 1998). However, it is not clear from the article how the anaesthetists made this assessment (evidence of overt penetration/aspiration during surgery as opposed to review of

chest x-ray post operatively) and no distinction was made between aspiration pneumonia and aspiration pneumonitis. It is possible this figure is under reported due to the incidence of silent aspiration in the anaesthetised patient.

Postoperative pneumonia is the third most common complication among surgical patients after urinary tract and wound infections (Wren, et al., 2010). A patient who has their surgical course complicated by aspiration has increased morbidity, increased length of hospital stay and places greater demands on the health system. In the intensive care setting, aspiration pneumonia can translate into additional healthcare costs of as much as US$40,000 per patient (Wren, et al., 2010). The prognosis for patients with postoperative pneumonia is poor (Wren, et al., 2010). Once diagnosed, aspiration pneumonia has a mortality rate between 20% and 70% (Wren, et al., 2010; Warner, Warner, & Weber, 1993).

Despite the prevalence of postoperative pneumonia and the high morbidity and mortality rates, not to mention the associated costs to the system, fairly little is known about the direct relationship between anaesthesia and the effects on cough reflex. Opioids are commonly given during anaesthesia to reduce perception of pain. It is possible that their action contributes to the clinical presentation of postoperative pneumonia by impairing cough: a known side effect.

Opiates are among the oldest drugs in the world (Brownstein, 1993; Trescot, Datta, Lee, & Hansen, 2008). Natural opiates are derived from the opium poppy, while synthetic opiates are specifically manufactured with a similar chemical structure. Natural and synthetic forms of opiates are collectively called opioids. The opioid system controls pain, reward and addiction (Kieffer & Gavriaux-Ruff, 2002). Side effects of opioids include sedation, respiratory depression, cough suppression, constipation and euphoria. The exact nature of respiratory depression remains unclear (LeGrand, et al., 2003). The generally accepted theory is that the respiratory centres housed in the medulla of the brainstem become less responsive

to states of hypoxia and hypercapnia (Saito, Sakura, Kaneko, & Kosaka, 1995). Another explanation, offered by LeGrand et al. (2003) is that opioids may influence the neurotransmitters of the medulla such as acetylcholine, 5-hydroxytryptamine, and noradrenaline. In terms of cough suppression, opiates are the most effective drugs for this purpose (Chung & Chang, 2002) and are the most commonly prescribed antitussives in chronic cough (Chung, 2007; Morice et al., 2007).

Prior to the 1800s, the use of opioids in surgery was haphazard. Sponges soaked in opium to decrease pain gave a variable rate of delivery/ absorbency and were dangerous (Brownstein, 1993). With the invention of the hypodermic syringe in the 1850's opioids began to be used as an adjunct to general anesthesia, both during and after to reduce pain perception and reaction to pain (Beilin, Shavit, Hart, Mordashov, Cohn & Notti et al., (1996). They continue to be used in this way today.

The analgesic effects of opioids occur by essentially blocking the transmission of pain to the brain. Opioids exert their action by binding to opioid receptors. There are three principle classes of opioid receptors: mu (μ), kappa (|) and delta (™) (Sigma-Aldrich, 1996). These opioid receptors are activated by endogenous opioid peptide genes: short sequences of amino acids. Each opioid receptor was named after the initial Greek letter of the drug that first bound to it. For example, morphine was first the first drug found to bind to mu receptors, depicted with the Greek 'm' symbol μ (Trescot et al., 2008).

Based on the initial finding of opioid receptors within the central nervous system (CNS) it was thought that opioids only acted centrally (Adcock, 1991) and that their effects on respiration and cough must also be brought about centrally. However, we now know that opioid receptors are present not only in the CNS, but also in the peripheral nervous system (PNS) including peripheral sensory and autonomic nerves (Sigma-Aldrich, 1996), the airway

and GI tract (Cabbott, 1994). Interestingly, the highest concentration of binding sites lie within the alveolar wall, tracheal and bronchial smooth muscle (LeGrand, et al., 2003).

Fentanyl

Pharmacology

Fentanyl citrate is a synthetic opioid analgesic chemically identified as N-(1-phenethyl-4—piperidyl) propionanilide citrate. It has a molar weight of 528.61 (AstraZeneca., 2012).

Indications for fentanyl include: use as short duration analgesia in anaesthesia (premedication, induction and maintenance) and in the immediate postoperative period, or as an analgesic supplement to regional or general anaesthesia (*MIMS New Ethicals*, 2012). Contraindications include: intolerance to morphinominetics, asthma, respiratory depression susceptibility e.g. coma with possible head injury or brain tumour, history of myasthenia gravis, MAOIs within 14 days (*MIMS New Ethicals*, 2012).

International guidelines generally recommend morphine or fentanyl as opioid medications for acute pain (Ward & Yealy, 2000). Fentanyl has similar action to morphine but is faster acting and has a shorter duration. Fentanyl's onset of action is approximately 3 minutes, versus morphine which takes approximately 10-15 minutes (Galinski et al., 2005). The duration of action of fentanyl is 30 minutes to 2 hours, whereas morphine has a duration of 3 to 4 hours (Galinski, et al., 2005). Fentanyl is much stronger than morphine; it is approximately 50-100 times as potent when compared mg to mg. For example, a dose of 100μg of fentanyl (0.1mg or 2.0mL) is equivalent in analgesic effect to 10mg of morphine (AstraZeneca., 2012). Fentanyl does not affect cardiac function or histamine release. The elimination half life of fentanyl is 114 minutes, whereas that of morphine is 185-220 minutes (Ward & Yealy, 2000).

Pharmacodynamics

Fentanyl is known to frequently decrease respiratory rate. The duration and degree of this depression is dose dependent. The peak effect of respiratory depression can be expected five to fifteen minutes post intravenous administration (AstraZeneca., 2012). The duration of respiratory depression may be longer than the analgesic effect. The NZ Fentanyl fact sheet describes decreased sensitivity to carbon dioxide ($C0_2$) stimulation up to four hours post 12ml (600µg) IV dose in healthy volunteers (AstraZeneca., 2012).

Pharmacokinetics

The onset and duration of action of any drug is affected by route of administration. When fentanyl is administered intravenously, its onset of action is almost immediate. Its maximum analgesic and CNS depressant effects last for several minutes. For a 100µg IV dose, the predicted duration of analgesia is 30-60 minutes (AstraZeneca., 2012).

Using mathematical modeling, scientists can estimate concentrations of drug in the plasma and effect site. The modeling is based on a mathematical generation known as a 'compartment model'. This concept essentially refers to a drug being injected into the 'central compartment' or plasma, then running to the 'peripheral compartment' (where first and second pass clearances will occur) and finally entering the 'effect compartment' or brain. Effect site concentration is a calculated apparent concentration of fentanyl at the brain receptors and is therefore the best surrogate of drug effect. The plasma concentration is a true measure of plasma concentration, however clinically it is more important to know the effect site concentration because that is where the drug acts. *"The concentration of a drug at the effect site, not the plasma concentration, governs the drug effect"* (Shafer & Varvel, 1991).

The pharmacokinetics of fentanyl are described by a three-component model: a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half life of 219

minutes (AstraZeneca., 2012). Fentanyl is routinely prescribed and administered across the perioperative period.

Summary

For the development of aspiration pneumonia there must be colonisation of oropharyngeal secretions, aspiration of this material into the airway (with or without food) and impaired patient resistance to clear the aspirated material. In the hospitalised patient, risk factors for all three conditions are increased. Typically, airway clearance is provided through the cough reflex, however the cough reflex is impacted by opioids and anaesthesia. Aspiration is a recognised complication of anaesthesia and postoperative pneumonia has mortality rates as high as 70% (Wren, et al., 2010). Hospital acquired pneumonia, including perioperative pneumonia, is the leading cause of nosocomial infection resulting in death in America (Tablan, Anderson et al., 2003). Despite these alarmingly high figures, very little research investigates clinically relevant means of identifying these patients and how to decrease their risk of postoperative aspiration.

One means of assessing the integrity of the vagally mediated cough reflex is through cough reflex testing. Significant relationships have been established between clinical application of cough reflex testing and reduction in pneumonia rates in the acute hospital setting (Miles, Zeng, et al., 2013; Nakajoh, et al., 2000). Studies have administered drugs (including opioids) to participants in an attempt to elucidate the effect they have on airway protective reflexes such as cough (Fuller, Karlsson, Choudry, & Pride, 1988; O'Connell, Thomas, Fuller, Pride, & Karlsson, 1994). However, none of these have included cough testing in a clinically applicable way in the post-surgical population. One major facet that appears to be missing from the literature is the time course for resolution of effects of opioids on the cough response. Clinically, it is important to know when the effects of cough

suppression attributable to anesthesia have worn off. This would aid the decision making of multidisciplinary teams in identifying which patients are safe to begin oral intake with intact airway protection in the event of aspiration, compared to those patients who continue to have impaired airway protection in the postoperative period.

Hypotheses

We hypothesised that:

1. As the intravenous dose of fentanyl was increased in the administration period, cough thresholds would increase and cough sensitivity would decrease. That is, a higher dose of citric acid would be required to elicit a cough response classed as ‘present’.
2. As the effect of fentanyl diminished with time in the post administration period there would be a time course for resolution of effects, including cough thresholds. That is, over time cough sensitivity would increase and cough response would return to baseline.

Chapter 2: Methodology

Participants

Following approval from the Southern Health and Disability Ethics Committee, the Canterbury District Health Board and the University of Canterbury Ethics Committee, healthy volunteers aged 18-70 were invited to participate in this study. The exclusion criteria were:

- Allergy to opioids
- History of asthma
- History of chemical addiction
- History of neurological impairment (e.g. stroke, Myasthenia Gravis)
- Use of nicotine 3 months prior to study
- Alcohol consumption 8 hours prior to study
- Use of MAOI antidepressants 14 days prior to study
- Any medical or nursing professional/ student who may have current or future access to fentanyl.
- Weight over 100kg.

Further to the exclusion criteria, our initial research protocol included an exit criterion, which stated that participants who met the inclusion criteria would be excluded if they failed to produce 2 strong consecutive coughs on 2/3 administrations (C2 response) at 0.8M citric acid nebulised via facemask (i.e. if they could suppress cough at this dose) on baseline assessment. The rationale for this was to monitor for return of cough response to baseline prior to departure. The choice of 0.8M citric acid as a 'cut off' was based on the

work of Manco, Bennett & Huckabee (2011) which found that 83.8% of the population have a natural cough response to 0.8M citric acid and that 91.9% of the population will generate a suppressed cough response at 0.9M citric acid.

Following the initial application of the protocol where a number of participants were excluded by the exit criterion, the research team removed this criterion and allowed each participant to act as their own control for the dose of citric acid required for them to produce 2 strong consecutive coughs on 2/3 administrations (C2 response). The range of citric acid used was 0.4M, 0.6M, 0.8M, 1.0M, 1.2M, 1.4M, 1.6M. The advantage of this change was that all participants who were eligible to participate in the study could be completed successfully and it allowed for normalisation of the data to each individual participant. As an example: if participant A had a baseline cough response at 0.4M citric acid, he would need to produce a C2 cough response at 0.4M prior to departure as a criteria of leaving. That is, would have returned to his suppressed cough response baseline.

A total of 17 healthy participants aged 18-44 gave informed written consent and were enrolled in the study. Three of these participants (1M1901, 7F0883, 8M0875) met the exit criteria described above prior to the change in protocol and are not included. Therefore, a total of 14 participants are included in data analysis (n=14). Characteristics are outlined in Table 1. The age range of participants was 22-44 years. The average age was 28.71 years (SD of 6.39). Five of the participants were male (35.7%), 7 were female (64.3%). Twelve of the participants identified as New Zealand European (85.7%), and two identified as European (14.3%). The height range of participants was 163-181cm. Average height was 171.5 cm (SD of 5.74). The weight range of participants was 57.7-91kg. Average weight was 57.7kg (SD of 11.48). Individuals' height and weight data were collected to determine dosing levels of fentanyl and to allow for generation of

dose-response curves. For exact dosing model, refer to 'administration period -calculation of fentanyl dose' (pg 37).

Table 1 Participant Characteristics

ID	Age (yrs)	Sex	Ethnicity	Height (cm)	Weight (kg)
2M0582	30	M	NZE	172	71.3
3F0790	22	F	NZE	168	63.6
4F0984	29	F	NZE	178	83.6
5M0778	34	M	NZE	170	91.0
6M0889	23	M	NZE	178	87.3
9F0281	32	F	NZE	170	76.9
10F0579	34	F	Eu	170	62.2
11M1078	34	M	NZE	175	78.6
12F0168	44	F	NZE	173	62.8
14M0589	24	M	NZE	181	82.8
15F1089	23	F	NZE	163	58.8
16F125 89	23	F	NZE	164	57.7
17F0390	23	F	NZE	163	59.6
18F0785	27	F	Eu	176	76.0

Procedure

Healthy participants attended the Gastroenterology Day Unit at Christchurch Hospital. This unit is designed to monitor patients post-surgical/ medical intervention. It is fully equipped with monitoring equipment, emergency equipment, resuscitation trolley and emergency call button to activate the ICU emergency response team.

For each participant, total participation time was 1.5- 2 hours. This was broken into 3 periods:

1. Pre-administration period
2. Administration period
3. Post-administration period

Pre-administration period

Participants were given a verbal explanation of what their participation involved and the written 'participant information sheet' (please see appendix A). They then had the opportunity to ask questions before signing the consent form (please see appendix B).

Basic recordings such as height and weight were taken as well as baseline recordings of oxygen saturation (Sa02), non-invasive blood pressure (NIBP), heart rate (HR) and respiratory rate (RR). These were displayed on the electronic monitors across the study and were recorded at 5-minute intervals as per hospital protocol to ensure patient vital stability.

Participants were directed to a bed space in the gastroenterology day unit. They remained comfortably semi-reclined on a bed throughout the pre-administration and administration phases.

Baseline suppressed cough response (BSCR) was measured and response recorded. A facemask connected to a DeVelbis Pulmomate nebuliser with a constant unobstructed flow

rate of 8L/min was placed over the participants' mouth and nose. Participants were asked to *"breathe in and out normally and to suppress the urge to cough"*. Solutions of citric acid diluted in 0.9% Sodium Chloride were prepared by the Christchurch Hospital Pharmacy at concentrations of 0.4M, 0.6M, 0.8M, 1.0M, 1.2M, 1.4M, 1.6M. The dosing began at the lowest citric acid concentration of 0.4M. Presentations then increased in increments of 0.2M, interspersed randomly with saline until a C2 response was obtained. Each dose was administered for a maximum of 15 seconds with a minimum of 30 seconds between each dose to prevent tachyphylaxis (Morice, 1996). Each dose was administered up to 3 times to ensure consistency of response. The response was categorised as present (2 strong coughs on 2/3 administrations) or absent (no cough on 2/3 administrations). Present responses were then rated as strong or weak. Each participant served as their own control for the dose of citric acid required for them to produce 2 present - strong responses on 2/3 administrations (C2 response). This baseline dose became the starting dose for each participant on each cough test.

Participants had an intravenous cannula inserted into their arm using subcutaneous lignocaine 0.1% under sterile conditions.

Administration period

Calculation of fentanyl dose.

Drugs were signed in and out of controlled drug cupboards by the study doctor and counter-signed by the study nurse according to national guidelines. Each participant received 4 titrated doses of IV fentanyl administered at intervals of 5 minutes. Each of the 4 doses was calculated at 0.5 mcg/kg and verified by a second researcher. The dosing model used to determine total dose was 0.5mcg fentanyl per kg (x 4). The maximum total dose a participant could receive (at a maximum weight of 100kg) was 200mcg fentanyl. Example dosages are below:

- For a 100kg participant = 0.5mcg x 100 x 4= 200 mcg total dose.
- For a 70 kg participant = 0.5mcg x 70 x 4 =140 mcg total dose.
- For a 50 kg participant = 0.5mcg x 50 x 4 = 100 mcg total dose.

Cough response

Suppressed cough response (SCR) was tested 3 minutes after each intravenous fentanyl administration. Testing began at the baseline citric acid dose for that individual. Presentations then increased in increments of 0.2M, interspersed randomly with saline and with a minimum of 30 seconds between trials until the C2 response was obtained using the method described above. If a participant elicited a present response (strong or weak) at a given dose of citric acid no higher doses of citric acid were tested. An absent response resulted in administration of higher doses, in increasing increments of 0.2M.

Post-administration period

In order to investigate the effects of fentanyl on cough reflex post-administration (as the effect site concentration was decreasing) cough response testing was continued. Each participant was tested at 10-minute intervals following administration of the final dose of fentanyl and subsequent cough testing (F4CRT) using the method described above.

Following Post4CRT, or return to baseline cough response, whichever came first participants were examined by the study doctor and if deemed medically stable, had their IV cannula removed and were disconnected from vital monitoring equipment. Participants were then directed to the recovery lounge in the Gastroenterology Day Unit where they were monitored. Their safety to leave under the supervision of a responsible adult as per Christchurch Public Hospital Protocol was determined by criteria below.

- Present strong cough response at individual baseline dose of citric acid (i.e. return to baseline)

- Assessed as meeting criteria by RN expert (e.g. stable vital signs, walk straight line)
- Responsible adult can assume care and drive participant home
- IV line removed
- Participant felt well enough to leave
- Participant had no further questions.

Table 2 Study protocol showing timing for participant A

Time	Action	Information
	Pre---administration period	
0800	Provision of information and consent.	
	Height and weight taken. Directed to bedspace.	
0815	Baseline cough response (BCR).	Beginning at 0.4M
0820	IV line sited by study doctor.	
	Vital sign monitor attached.	Sp02, HR, RR, NIBP
0825	Vital signs recorded.	
	Administration period	
0830	**First administration of fentanyl (F1)**	
	Record all 4 vital signs (RR, HR, Sa02, NIBP)	
0833	Cough response post F1 (F1CRT)	Starting from baseline dose
0835	**Second administration of fentanyl (F2)**	
	Record all 4 vital signs (RR, HR, Sa02, NIBP)	
0838	Cough response post F2 (F2CRT)	Starting from baseline dose
0840	**Third administration of fentanyl (F3)**	
	Record all 4 vital signs (RR, HR, Sa02, NIBP)	
0843	Cough response post F3 (F3CRT)	Starting from baseline dose
0845	**Fourth administration of fentanyl (F4)**	
	Record all 4 vital signs (RR, HR, Sa02, NIBP)	

0848	Cough response post F4 (F4CRT)	Starting from baseline dose
	Post administration Period	
0850	Record all 4 vital signs (RR, HR, Sa02, NIBP)	
0900	Cough response--- Post1CRT	Starting from baseline dose
0910	Cough response--- Post2CRT	Starting from baseline dose
0920	Cough response--- Post3CRT	Starting from baseline dose
0930	Cough response--- Post4CRT	Starting from baseline dose
0932	Reviewed by study physician. If medically stable IV line and monitors removed.	
	Directed to recovery area/ lounge.	
	Monitored by study nurse. Leave once exit criteria met.	

Data and Statistical Analysis

Statistical analyses were completed using Statistical Package for the Social Sciences Inc. (SPSS version 21, release 21.0.0). A p value <0.05 was considered statistically significant. Descriptive statistics were initially performed to establish mean and standard deviation data for both effect site concentration (ESC) and cough reflex testing (CRT). Following this, we calculated the increments of change in CRT (M). Pearson's correlation co-efficient (r) was conducted to determine the relationship between mean increments of CRT change (M) and mean effect site concentration (ng/ml). Lastly, a paired samples t-test was conducted to compare cough response thresholds between two conditions: baseline CRT and peak CRT. The analyses were based on increments of change with one increment equaling 0.2M.

Effect site concentrations were established using AnesstAssist©**.** This is a computer generated modeling system which calculates estimates of drug effect site and plasma concentrations and probabilities of effects using mathematical models published in peer reviewed journals (Palma, 2009). There are 2 mathematical models used for calculating the pharmacokinetic and pharmacodynamics properties of intravenously administered Fentanyl in AnestAssist© (Palma, 2009). The first is that of Scott & Stanski (1987) which does not include co-variates such as age, gender, height. The second model derived by Shafer & Varvel (1991) accounts for co-variates and is the standard fentanyl pharmacokinetic model used by anaesthetists and clinical researchers. The model includes a triexponential equation:

$$Cp(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-17t}$$

In this equation C_p represents plasma concentration; t represents time; A, B, C are coefficients describing the relative contributions; α represents rapid-distribution half life; β represents slow-distribution half life and ϒ represents elimination half life.

Chapter 4: Results

Both ESC and cough threshold are ratio and interval variables respectively. They both have an absolute zero point. They are quantitative numbers and are suitable for parametric tests. Therefore, mean (rather than median) data are reported.

Effect site concentration (ESC)

As shown in table 3, the ESC mean and standard deviations were calculated. The mean ESC between participants was similar at each assessment point. Standard deviations ranged between 0.01 and 0.27ng/ml. This small range is attributed to the individualized fentanyl dosing-model employed. Each dose of fentanyl was calculated based on participant weight at 2mcg x kg (with a maximum total dose of 200mcg) rather than set doses of 50mcg per bolus. As discussed, AnestAssist© (Palma, 2009) was the modeling system used to calculate each participant's fentanyl ESC.

Table 3 Mean ESC at each assessment point

	ESC (ng/ml)	
	Mean	SD
Baseline	0.00	0.00
F1CRT	0.65	0.02
F2CRT	1.17	0.03
F3CRT	1.57	0.03
F4CRT	1.89	0.05
Post1CRT	1.15	0.03
Post2CRT	0.80	0.02
Post3CRT	0.67	0.27
Post4CRT	0.48	0.01

In the pre-administration period (baseline) ESC was zero. During the administration period (F1CRT-F4CRT) there was a constant increase in the mean ESC, with mean peak ESC at F4CRT, immediately post final dose of fentanyl. In the post-administration period (Post1CRT-Post4CRT) there was a steady decrease in mean ESC values. Of note is the

finding that at Post4CRT (forty minutes post final administration of fentanyl) ESC ranged between 0.47-0.49ng/ml, it had not returned to zero. Using the pharmacokinetic model to predict how long it would take to return to an ESC of between 0.00-0.05ng/ml based on 2mg/kg given at 5-minute intervals, all participants were estimated to take at least 1 hour and forty minutes.

Cough reflex testing (CRT)

Table 4 Mean cough response at each assessment point

	Cough Response (M)	
	Mean	SD
Baseline	0.50	0.28
F1CRT	0.60	0.43
F2CRT	0.70	0.43
F3CRT	0.90	0.43
F4CRT	1.20	0.50
Post1CRT	1.00	0.51
Post2CRT	0.80	0.51
Post3CRT	0.70	0.45
Post4CRT	0.50	0.29

Each individual acted as their own control for suppressed cough reflex testing, the mean baseline response was 0.5M (min=0.4M, max= 1.4M, range=1.0M). Interestingly, 12 participants had a suppressed baseline cough response at 0.4M. One participant (14M0589) did not change from his baseline dose. At all assessment points he had a present-strong response to 0.4M citric acid. He was removed from further cough response group analysis from this point onwards, therefore n= 13. Standard deviations at all assessment points were very tight, ranging between 0.0 and 0.54M. During the administration period (F1CRT-F4CRT) there was a constant increase in the mean CRT, with mean peak CRT at F4CRT, immediately post final dose of fentanyl. In the post- administration period (Post1CRT-Post4CRT) there was a steady decrease in mean CRT values.

Increments of CRT change

The majority of participants (76.92 %) had their peak cough threshold in F4CRT (mean cough threshold of 1.20M compared to mean 0.5M baseline). The effect site concentration of F4CRT was also the highest at this assessment point, at 1.89ng/ml. The second highest cough thresholds occurred in F3CRT (mean cough threshold 0.9M), with effect site concentrations at 1.57ng/ml. Therefore, at the highest ESC of fentanyl, cough sensitivity was the lowest. The largest mean number of increments of change in cough threshold occurred in F4CRT as shown in figure 5.

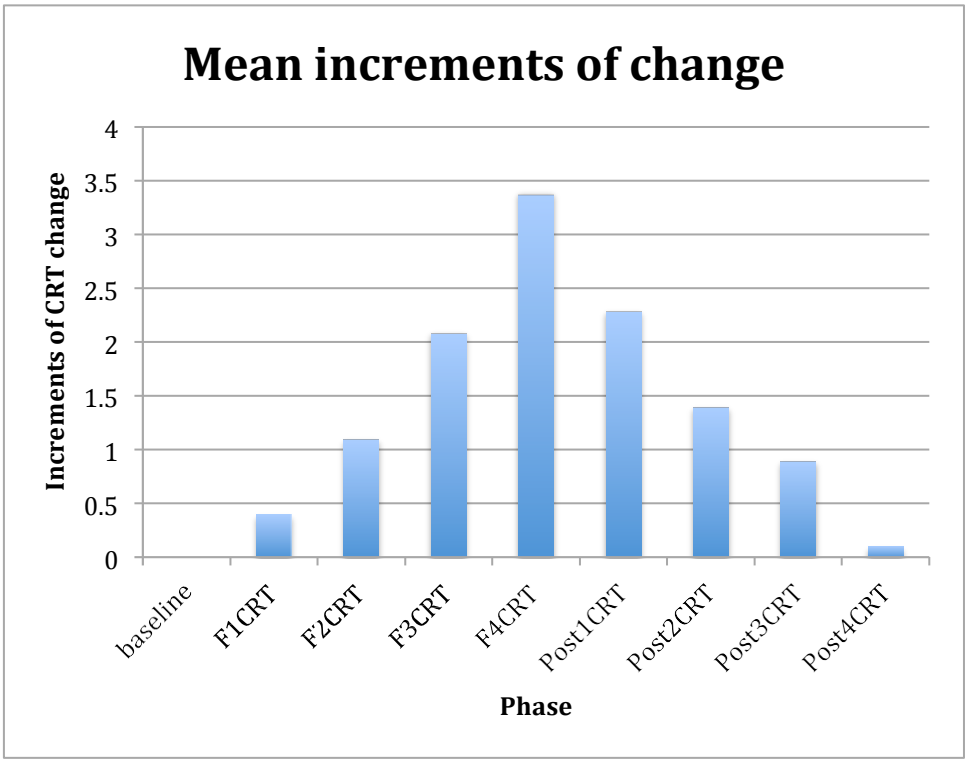

Figure 4. Mean increments of cough reflex change.

Pearson's correlation co-efficient was conducted to determine the relationship between mean increments of CRT change (M) and mean effect site concentration (ng/ml). A positive correlation was found between the two variables at the 2-tailed level [r=9.19, n=9, p= <0.01].

As detailed in the methods section, doses of citric acid ranged between 0.4M and 1.6M, in increasing doses of 0.2M; giving a total of 7 doses of citric acid, with a range of 1.2M citric acid. Of the 13 participants who had a change in their cough threshold from baseline, 5 increased by 6 or more units of citric acid (ceiling was reached at 1.6M), 1 had a change of 5 units of citric acid, 1 had a change of 4 units and the other 5 participants had a change of 3 or less units. In figure 5, red columns indicate ceiling was reached at our highest dose of 1.6M citric acid.

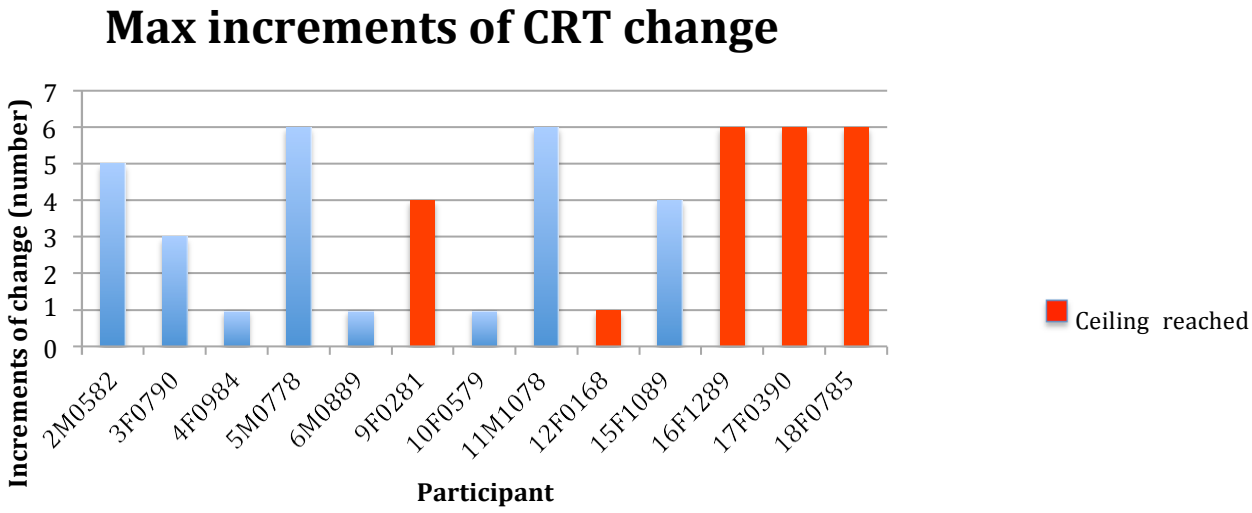

Figure 5. Maximum increments of CRT change.

A paired samples t-test was conducted to compare cough response thresholds between two conditions: baseline CRT and peak CRT [t= -5.701, df=13, p=<0.01]. There was a significant difference in the scores of baseline CRT (M=0.5, SD 0.28) and peak CRT (M=1.21, SD= 4.7).

The period in which participants returned to their own baseline was also calculated. Participants appear to either have returned to baseline rather rapidly (28 % returned to their own baseline in Post1CRT) or not until the final assessment (29% returned in Post4CRT). Fewer participants returned in the middle of the post assessment period (Post2CRT and

Post3CRT). One participant (17F0390) required an extra assessment CRT, labeled as 'ExtraPsot5CRT,' 50 minutes post final fentanyl administration to return to her own CRT baseline of 0.4M. Refer to figure 6.

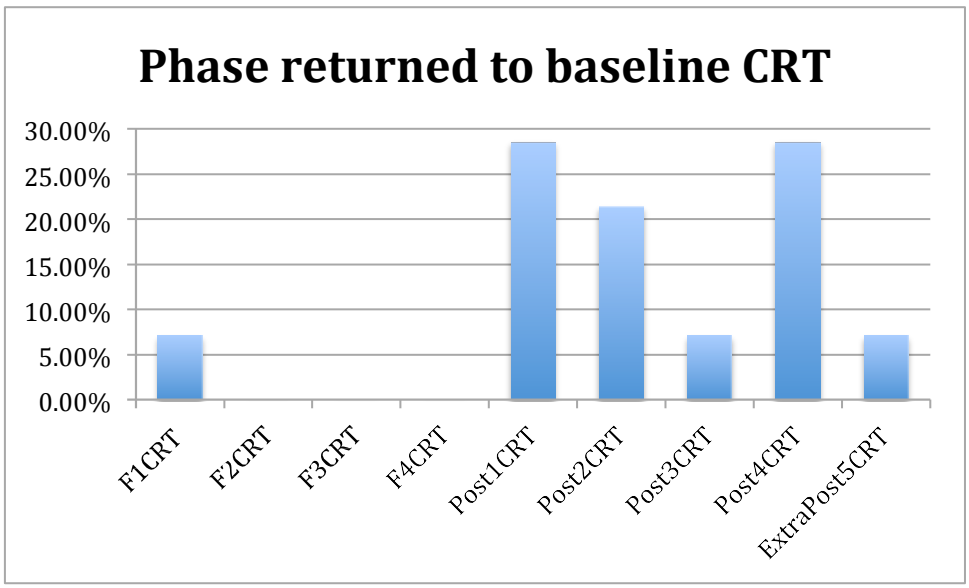

Figure 6. Period returned to baseline CRT, by percentage.

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Chapter 5: Discussion

Baseline cough thresholds

The majority of participants had a baseline suppressed cough response at 0.4M. This threshold is lower than suppressed threshold levels reported in previous studies. Because our participants were healthy volunteers, the most appropriate studies for comparison are normative studies employing the same method. Normative studies by necessity have extensive exclusion criteria, as did our study. In their investigation, Monroe (2010) reported 70% of their healthy participants elicited a SCR at 0.8M. However, their dosing range was 0.8M- 2.6M and they found a significant flooring effect, whereby participants may have had a present response to doses of citric acid lower than 0.8M had they been administered. Manco (2011) addressed this flooring effect by collecting normative data with a testing range between 0.1M and 1.2M. Despite testing at substantially lower does, they actually reported 91.9% of participants had SCT at 0.9M- higher than the dose initially reported by Monroe (2010). Our data set was small and it is possible our median baseline dose of 0.5M may have increased with a larger sample size.

Fentanyl effect on CRT

Our results support the findings of previous studies that show a clear reduction in cough strength sensitivity following intravenous administration of opiates (Tagaito, et al., 1998; O'Connell, 2002; Fuller, et al., 1988). To our knowledge there are no identified studies that systematically investigate the cough reflex as the opioid effect site concentration is decreasing. This is perhaps where the clinically applicable information lies. We know that opioids decrease cough sensitivity, what needs further elucidation is to what extent and for what period of time. Clinically, this may help direct postoperative monitoring regimes in the future, including the assessment of which patients are safe to being eating and drinking across

the perioperative period. Current clinical protocols for resumption of oral intake postoperatively are site-specific and staff dependent. Pneumonia prevention programs have successfully been implemented in ICU settings, but no such protocols are in place for surgical wards (Wren, et al., 2010). Clinically, if a patient is deemed alert enough to eat then staff may commence them on an oral diet as early as in the recovery or post anaesthetic care unit. Unfortunately, those patients most at risk of developing postoperative aspiration pneumonia related to an impaired cough response may not show any overt signs of aspiration and will go undetected at bedside. The application of a screening test in the postoperative population may assist in identifying high-risk patients who require either a longer period of recovery time for resolution of cough suppression, or a referral to speech language therapy prior to resumption of oral intake.

Strengths and limitations

The strengths of this study include: the fentanyl dosing model of 2mcg/kg and the use of a pharmacokinetic model to determine effect site concentrations in the brain. Studies conducted on psychoactive drugs (e.g. fentanyl) cannot be completely blinded because the subject is conscious of the effects (Morice, et al., 2007). Participants must of course give informed consent to contribute to studies involving medicines, and as a result are necessarily informed of the potential effects. A blinded study where all participants consented to administration of fentanyl but a randomly assigned control group were administered a placebo could have improved this. Weaknesses of this study include: participants' awareness during the administration period that fentanyl was being dispensed to them and in the post-administration period that it was not. This may have impacted volitional cough suppression and could have been controlled for by blinding and/ or placebo administrations.

In an attempt to correct for some supramedullary impact on the assessment of cough reflex, suppressed cough response was used and presentations of citric acid were interspersed with saline. Participants were instructed to 'try not to cough'. This may in fact represent a

reflex thresholds are higher than natural cough thresholds and although baseline suppressed cough threshold was lower than previously reported studies; a ceiling was reached at 1.6M.

This was a pilot study investigating young, healthy participants with extensive exclusion criteria. The application of these data directly to the postoperative population is not possible because of these factors. The average surgical patient is likely to be older and have co-morbidities not accounted for in this study. For example, a recent study reported on 2,448 patients undergoing hip surgery; mean age was 82 years with 35% having at least one comorbidity (Roche, Wenn, Sahota, & Moran, 2005). However, cough reflex testing has been shown to correctly identify those patients who are at risk of silent aspiration (Addington, et al., 1999; Miles, Moore, et al., 2013). Cough testing is simple to administer and these results suggest further investigation into use in the postoperative setting is warranted.

Future directions

In order to apply results generated from this research into clinical practice, normative data of suppressed cough thresholds would need to be generated in the preoperative and postoperative populations. It would then be reasonable to conduct a larger scale study comparing postoperative pneumonia rates in a sample of patients who received cough testing compared to a control group who received standard postoperative care.

Given the large role altered oropharyngeal flora plays in the development of aspiration pneumonia, another area of research that may benefit from investigation is the application of a strict oral hygiene protocol in preoperative and postoperative patients.

Conclusion

This study is unique in identifying the effect of fentanyl on suppressed cough reflex post administration of a clinically relevant dose of 2 mcg/kg. The finding that cough reflex testing is sensitive enough to parallel changes in fentanyl effect site concentration in the brain is exciting and opens a potential area of clinical application in the postoperative population.

The degree of reflex suppression seen in this study has been associated with a 8-fold increase in aspiration risk in the dysphagic general medical population, where patients with an abnormal response to 0.8M of citric acid had an odds ratio for silent aspiration of 8.0 (Miles, Moore, et al., 2013). Further research into the application of SCR in the post operative period may help identify those at particular risk of pulmonary complications and direct more intensive monitoring and alternative analgesic regimes. This would provide substantial health and cost benefits and improve patient outcomes.

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Appendices

Appendix A: Participant Information Sheet

Participant Information Sheet

Study title:	***The effect of Fentanyl on swallowing and cough response***	
Locality:	**CDHB**	Ethics committee ref.: **12/NTB/39**
Lead investigator:	**Dr Geoffrey Shaw**	Contact phone number: **03 364 1077**

You are invited to take part in a study on the effect of fentanyl on swallowing and cough response. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason. If you do want to take part now, but change your mind later you can withdraw from the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It explains why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. This will take about 15 minutes. You may also want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep. Participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue. This document is 7 pages long including the Consent Form. Please make sure you have all the pages.

Why are we doing the study?

When people undergo surgery, drugs are given to sedate them. Often they are also given drugs to help reduce pain. These drugs are called opioids. One such opioid is fentanyl. Fentanyl can affect breathing and cough.

During and after surgery, people still swallow their saliva even if they are not eating and drinking. In healthy people there is a set pattern to breathing and swallowing. This is called swallowing respiratory coordination. It helps stop food, drink and saliva from going in to the lungs when we eat. Breathing at the wrong time during swallowing can be a problem. When swallowed material goes 'the wrong way' it may go into the lungs, this is called aspiration. This can cause injury to the delicate air sacs in the lung. One way to protect our bodies from aspiration is to cough. Coughing forces material out of the lungs so that it can be re-swallowed. A reduced cough response reduces the ability to keep our lungs clean.

We will look into the how fentanyl changes swallowing respiratory coordination and cough response. Both these functions are easily measured. Healthy participants will be asked to attend one session. An intravenous (in-vein, IV) cannula will be inserted. Each participant will receive four injections of fentanyl into the vein. Cough response to breathing in a mist of dilute citric acid (the sour part of lemon juice) and swallowing respiratory coordination will be measured after each injection. This will help us to understand what happens to people's swallowing and cough function during and after surgery.

We do not know how much fentanyl affects our ability to swallow and cough correctly. We also do not know if some people having surgery are much more sensitive to the effects of fentanyl, which might increase their chance of aspiration and lung injury. This study will help us learn more about this problem so that we can improve the safety and care of patients who need fentanyl for relief of their pain. This study has been approved by the Southern Health and Disability Ethics Committee and the University of Canterbury Committee.

Who is conducting the study? Co-ordinating investigator:

Dr Geoffrey Shaw, MBChB, FANZCA, FCICM , Intensive Care Specialist, Department of Intensive Care, Christchurch Hospital, Senior Clinical Lecturer, Department of Anaesthesia, University of Otago, Department of Intensive Care, Christchurch Hospital ,Christchurch, New Zealand. Phone: (03) 364 1077. E-mail: geoff.shaw@cdhb.health.nz.

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Helana Kelly, Master's student, University of Canterbury, Ba App Sc (Speech Pathology), Speech Language Therapy Department, Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand. Phone:(03) 364 1464.E-mail: helana.kelly@cdhb.health.nz.

Faye Greenwood, RN, Registered Nurse (Expert), Post-Anaesthetic Care Unit**,** Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand. Phone: (03) 364 0640**.** Email: faye.greenwood@cdhb.heath.nz.

Who can participate?

Up to 20 healthy participants aged 18-70 will be asked to participate.

Exclusion criteria:

- Allergy to opioids
- History of asthma
- History of chemical addiction
- History of neurological impairment (e.g. stroke, Myasthenia Gravis)
- Use of nicotine 3 months prior to study
- Alcohol consumption 8 hours prior to study
- Use of MAOI antidepressants 14 days prior to study
- Any medical or nursing professional/ student who may have current or future access to fentanyl.
- Weight over 100 kg

What would your participation involve?

You are invited to attend 1 session. It will take 1.5-3 hours. The study will be completed at:

Gastroenterology Day Unit

Level 1 Riverside

Christchurch Public Hospital

Riccarton Avenue, Christchurch 8041.

This site is fully equipped with emergency equipment. The coordinating investigator is an intensive care specialist. The co-researcher is a registered nurse. If you consent, the following will occur:

Insertion of an Intravenous IV line

- A tourniquet (band) will be applied to your upper arm.
- The doctor will insert an intravenous IV cannula into your arm.

- This can be uncomfortable for a short period.

Administration of the drug Fentanyl

- The doctor will administer 4 doses of fentanyl.
- They will be 5 minutes apart.
- They will be given through your intravenous IV cannula.

Assessment of Cough Response (CR)

- You will place a plastic mask over your mouth and nose.
- A small chamber connected to the mask will be filled with different concentrations of citric acid.
- This citric acid will be turned into a mist by a small device that forces air through it.
- You will breathe in and out for 15 seconds (maximum).
- This may cause you to want to cough.
- You will be asked to try and suppress (hold back) your cough.
- It can be mildly uncomfortable for a few seconds.
- You will have break of 30 seconds between each administration.

Removal of Intravenous IV line

- A registered nurse will remove the IV cannula.
- This may cause mild discomfort for a few seconds.

Monitoring

A registered nurse will monitor you during the study. Before you leave you will have:

- A final cough response (CR) test.
- Stable vital signs (including heart rate, blood pressure).
- A responsible adult to drive you home.
- A responsible adult at home.

What are the possible benefits and risks to you of participating?

There are no known risks associated with assessing swallowing respiratory coordination (SRC) or cough response (CR) in healthy people. There are some possible side effects of fentanyl.

These are listed below.

Common: Feeling “high”, mild nausea, slowed breathing and heart rate.

Less common: Low blood pressure, very slow breathing, blurred vision, small pupils, nausea, and dizziness

Rare: Jerky or stiff muscles, sweating, allergic reactions (resulting in wheezing, a rash and/or very low blood pressure), hypoventilation

A doctor and nurse will monitor you closely. In the very unlikely event of any serious side effects, appropriate medications and equipment will be immediately available.

Participation will not benefit you directly. You will be assisting in research to improve health outcomes. Participation will not cost you anything. You will receive no reimbursement. Fentanyl will not be available to you after the study. It is administered for research purposes only.

What would happen if you were injured in the study?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home.
If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

What are the rights of participants in the study?

Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason. It won't affect the care you receive now or in the future. If you do want to take part now, but change your mind later, you can withdraw from the study at any time.
No material that could personally identify you will be used in any reports on this study. You are entitled to a copy of your data on request.

What will happen after the study ends, or if you pull out?

You will be offered copies of the final publication of this project, or a summary in plain English. There will be no associated cost. However, the final publication will not be available for up to 18 months.
Consent forms will be kept in a locked filing cabinet in the New Zealand Brain Research Institute. With your permission, de-identified (anonymous) research data will be stored on a computer so this material will be available for future researchers. These future studies that use this data may need to seek approval from a Health and Disability Ethics Committee.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Dr Geoffrey Shaw
Intensive Care Specialist

Phone: (03) 364 1077

E-mail: geoff.shaw@cdhb.health.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050

Fax: 0800 2 SUPPORT (0800 2787 7678)

Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

You can also contact Christchurch Hospital Māori Health Services (Nga Ratonga Hauora Māori) on:

Phone: (03) 364 0640

Fax: (03) 3786018

Appendix B: Participant Consent Form

Consent Form

Request for interpreter

English	I wish to have an interpreter	Yes	No
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

Declaration by participant:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. I have had the opportunity to ask questions and I am satisfied with the answers I have received.I freely agree to participate in this study. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it. I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

Appendix C: Summary Data Tables

Summary table- Individual cough responses (CRT)

Participant	Baseline CRT (M)	F1CRT (M)	F2CRT (M)	F3CRT (M)	F4CRT (M)	Post1CRT (M)	Post2CRT (M)	Post3CRT (M)	Post4CRT (M)
2M0582	0.4	0.6	1.0	1.2	1.4	1.0	0.8	0.6	0.4
3F0790	0.4	0.4	0.8	1.0	1.0	1.0	0.4	0.4	0.4
4F0984	0.4	0.4	0.4	0.4	0.6	0.6	0.4	0.4	0.4
5M0778	0.4	0.4	0.8	0.8	1.6	0.4	0.4	0.4	0.4
6M0889	0.4	0.4	0.4	0.6	0.4	0.4	0.4	0.4	0.4
9F0281	0.8	1.6	1.6	1.6	1.6	1.6	1.6	1.6	0.8
10F0579	0.4	0.4	0.4	0.4	0.6	0.4	0.4	0.4	0.4
11M1078	0.4	0.4	0.6	1.4	1.6	1.4	0.4	0.4	0.4
12F0168	1.4	1.6	1.6	1.6	1.6	1.4	1.4	1.4	1.4
14M0589	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
15F1089	0.4	0.4	0.4	0.8	1.2	0.4	0.4	0.4	0.4
16F1289	0.4	0.4	0.4	0.8	1.6	1.6	1.4	0.4	0.4
17F0390	0.4	0.4	0.4	0.6	1.6	1.6	1.6	1.4	0.8
18F0785	0.4	0.4	0.8	1.2	1.6	1.2	1.0	0.8	0.4
MEAN	**0.5**	**0.6**	**0.7**	**0.9**	**1.2**	**1.0**	**0.8**	**0.7**	**0.5**

Summary table- effect site concentrations (ESC)

Participant	ESC F1CRT (ng/ml)	ESC F2CRT (ng/ml)	ESC F3CRT (ng/ml)	ESC F4CRT (ng/ml)	Post1CRT (ng/ml)	Post2CRT (ng/ml)	Post3CRT (ng/ml)	Post4CRT (ng/ml)
2M0582	0.67	1.2	1.57	1.94	1.21	0.83	0.62	0.49
3F0790	0.66	1.19	1.56	1.92	1.14	0.81	0.60	0.49
4F0984	0.66	1.18	1.57	1.91	1.16	0.83	0.61	0.49
5M0778	0.65	1.15	1.54	1.87	1.11	0.78	0.60	0.48
6M0889	0.64	1.14	1.53	1.85	1.13	0.77	0.59	0.47
9F0281	0.63	1.1	1.52	1.77	1.11	0.78	0.58	0.46
10F0579	0.64	1.16	1.57	1.89	1.15	0.81	1.61	0.48
11M1078	0.66	1.19	1.59	1.92	1.15	0.80	0.60	0.49
12F0168	0.63	1.14	1.54	1.81	1.14	0.79	0.58	0.47
14M0589	0.67	1.2	1.61	1.93	1.20	0.82	0.63	0.49
15F1089	0.66	1.19	1.58	1.92	1.19	0.81	0.60	0.49
16F1289	0.68	1.21	1.62	1.96	1.19	0.84	0.62	0.50
17F0390	0.65	1.14	1.57	1.89	1.14	0.79	0.58	0.48
18F0785	0.64	1.15	1.55	1.87	1.12	0.79	0.59	0.47
MEAN	**0.65**	**1.17**	**1.57**	**1.89**	**1.15**	**0.80**	**0.67**	**0.48**
SD	**0.02**	**0.03**	**0.03**	**0.05**	**0.03**	**0.02**	**0.27**	**0.01**

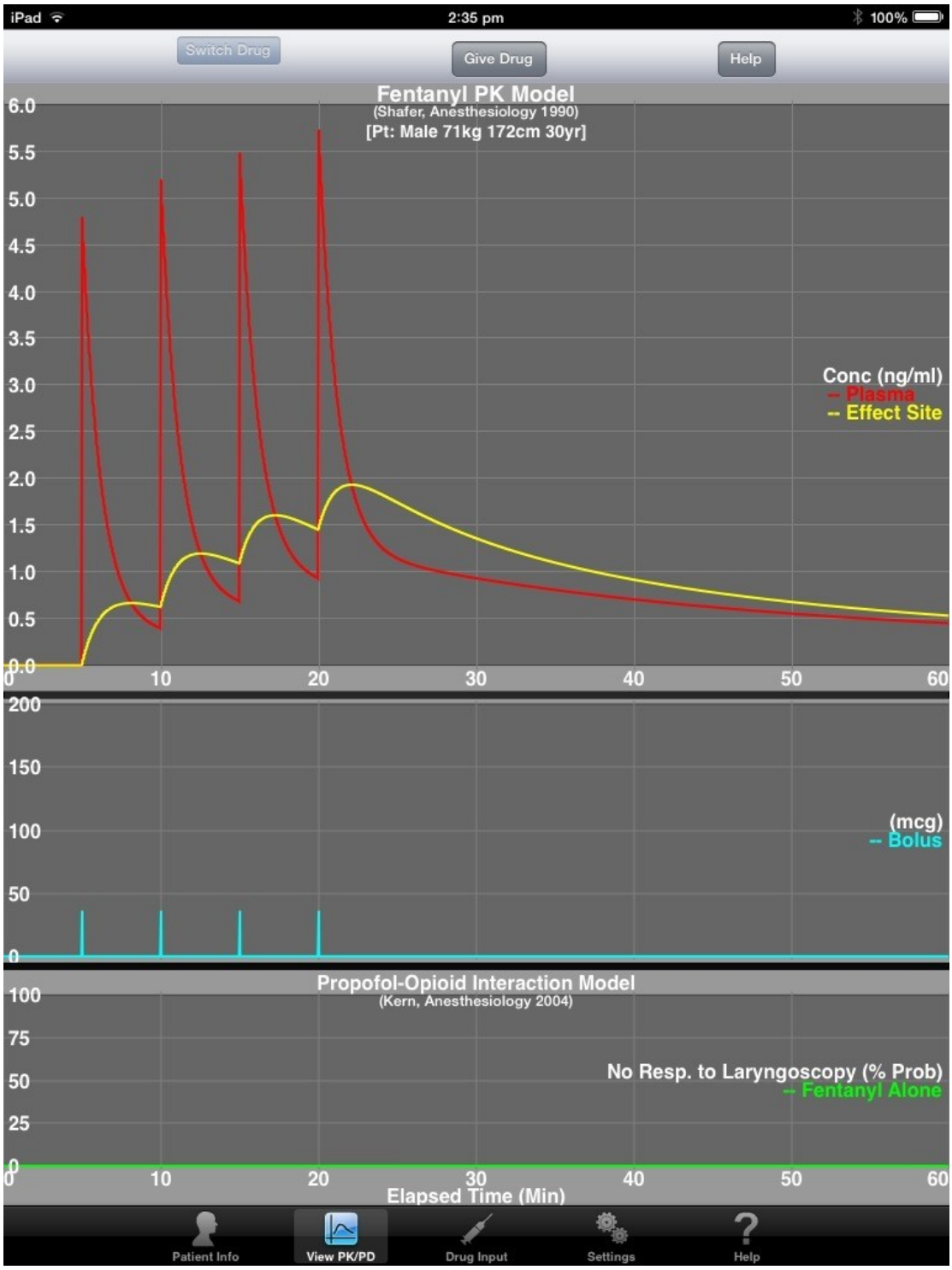
Summary table- mean increments of cough (CRT) change

Participant	Baseline CRT (M)	F1CRT Increments change	F2CRT Increments change	F3CRT Increments change	F4CRT Increments change	Post1CRT Increments change	Post2CRT Increments change	Post3CRT Increments change	Post4CRT Increments change
2M0582	0.4	1	3	4	5	3	2	1	0
3F0790	0.4	0	2	3	3	3	0	0	0
4F0984	0.4	0	0	0	1	1	0	0	0
5M0778	0.4	0	2	2	6	0	0	0	0
6M0889	0.4	0	0	1	0	0	0	0	0
9F0281	0.8	4	4	4	4	4	4	4	0
10F0579	0.4	0	0	0	1	0	0	0	0
11M1078	0.4	0	1	5	6	5	0	0	0
12F0168	1.4	1	1	1	1	0	0	0	0
14M0589	0.4	0	0	0	0	0	0	0	0
15F1089	0.4	0	0	2	4	0	0	0	0
16F1289	0.4	0	0	2	5	6	5	0	0
17F0390	0.4	0	0	1	6	6	6	5	2
18F0785	0.4	0	2	4	6	4	3	2	0
Mean Increments Change	**0.0**	**0.4**	**1.1**	**2.1**	**3.4**	**2.3**	**1.4**	**0.9**	**0.1**

Appendix D: Example Computer Generated ESC

Individual effect site concentration (ESC) generated by AnnestAssist™

Example based on participant 2M0582



Appendix E: Physiological Data Summary Tables

Physiological data-Respiratory Rate (RR)

Participant	BaseRR	F1RR	F2RR	F3RR	F4RR	Post1RR	Post2RR	Post3RR	Post4RR
2M0582	13	13	11	12	12	12	12	11	12
3F0790	15	13	M	M	M	M	M	M	M
4F0984	15	13	M	M	M	M	M	M	M
5M0778	12	12	14	12	12	12	10	10	10
6M0889	14	14	12	12	10	10	10	12	12
9F0281	16	16	16	14	14	14	12	12	12
10F0579	16	18	20	20	18	16	16	14	M
11M1078	16	14	12	12	14	14	16	16	14
12F0168	16	16	16	14	14	12	9	10	8
14M0589	16	18	16	12	10	10	10	12	14
15F1089	16	12	12	10	10	12	16	10	8
16F1289	16	14	14	14	14	12	10	10	12
17F0390	12	14	14	14	10	10	8	8	10
18F0785	14	14	12	12	12	8	10	7	6

Physiological data- Arterial Oxygen Saturation (Sa02)

ID	F1Sa02	F2Sa02	F3Sa02	F4Sa02	Post1Sa02	Post2Sa02	Post3Sa02	Post4 Sa02
2M0582	97	97	97	96	94	95	96	97
3F0790	98	97	96	95	95	96	96	M
4F0984	100	100	96	100	100	99	M	M
5M0778	96	96	97	97	97	94	95	96
6M0889	100	100	97	95	96	97	99	99
9F0281	96	96	96	96	97	97	96	96
10F0579	100	100	100	99	99	96	98	M
11M1078	99	98	98	97	97	97	97	98
12F0168	100	100	100	100	100	100	100	99
14M0589	96	96	97	94	92	94	92	95
15F1089	98	98	98	98	98	99	98	96
16F1289	99	99	99	96	97	96	96	96
17F0390	97	98	100	98	99	100	100	98
18F0785	97	98	98	97	96	97	94	96

Physiological data- Blood Pressure (BP)

	Base		F1		F2		F3		F4		Post1		Post2		Post3		Post4	
Participant	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
2M0582	118	78	142	82	135	95	139	90	144	92	145	95	143	85	135	85	135	85
3F0790	110	65	98	60	105	74	115	74	121	69	117	73	114	65	110	66	M	M
4F0984	150	80	139	74	136	75	115	85	140	85	152	74	140	66	M	M	M	M
5M0778	122	78	115	76	118	76	135	79	127	75	132	75	140	84	139	85	134	74
6M0889	130	80	129	94	108	75	120	75	120	75	112	75	118	85	105	68	109	74
9F0281	124	73	138	76	135	81	139	86	144	95	135	79	109	80	135	75	139	70
10F0579	132	86	159	86	150	90	140	86	140	76	140	85	129	78	133	80	M	M
11M1078	105	32	85	39	84	44	85	54	85	52	86	52	90	58	100	61	105	60
12F0168	130	90	118	83	126	78	121	80	124	84	129	94	116	83	133	79	119	83
14M0589	129	66	110	56	120	56	120	55	115	60	120	51	120	53	125	60	110	58
15F1089	105	60	103	60	103	64	92	60	92	60	105	45	106	45	106	56	105	58
16F1289	120	80	123	84	125	82	125	82	110	75	120	81	119	80	120	80	115	75
17F0390	112	75	105	82	115	70	120	70	132	77	125	80	132	70	107	70	113	78
18F0785	105	55	110	70	126	74	120	69	119	80	119	76	130	70	122	70	124	64

Physiological data- Heart Rate (HR)

ID	BaseHR	F1HR	F2HR	F3HR	F4HR	Post1HR	Post2HR	Post3HR	Post4HR
2M0582	77	80	90	90	85	85	85	70	70
3F0790	85	75	85	85	85	90	70	70	M
4F0984	115	120	105	120	125	120	105	M	M
5M0778	65	60	75	80	85	80	65	65	70
6M0889	65	55	75	65	70	55	65	55	55
9F0281	90	95	95	95	95	105	90	105	105
10F0579	100	115	125	110	100	100	85	95	M
11M1078	60	50	65	65	75	80	80	55	50
12F0168	110	85	105	95	95	90	85	90	82
14M0589	75	75	85	75	70	75	75	65	65
15F1089	80	80	75	80	80	95	100	80	75
16F1289	115	120	130	135	110	105	105	105	105
17F0390	105	105	105	110	105	115	105	85	95
18F0785	70	80	85	80	95	90	80	95	95