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Current Topics in Medicinal Chemistry, 2015, *15*, 939-954

Design and Development of a Novel Supportive Care Product for the Treatment of Sialorrhea in Parkinson's Disease

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Abstract: Sialorrhea or excessive drooling is a significant medical issue in Parkinson's disease (PD) and neurodegenerative disorders, although it is often underreported by patients. Sialorrhea affects a large proportion of PD patients, ranging up to 78% in advanced stages, with many PD patients considering drooling as their worst non-motor symptom. Sialorrhea affects up to a million patients with diverse neurological impairments, including cerebral palsy, amyotrophic lateral sclerosis (ALS), Huntington's, survivors of stroke and severe traumatic brain injury. Numerous approaches have been attempted to treat sialorrhea in PD patients, including surgical procedures, prosthetic devices, botulinum injections, systemic anticholinergic drugs, and speech and behavioral therapy. A novel drug treatment (NH004) to control the symptoms of sialorrhea is under development. The active ingredient is the anticholinergic drug tropicamide. Anticholinergic drugs work by blocking acetylcholine muscarinic receptors and ultimately decreasing saliva secretion via the reduction of parasympathetic autonomic nervous system activity. The tropicamide is delivered in a thin film designed to adhere to the buccal mucosa and to slowly dissolve within the oral cavity, allowing the drug to reach the underlying salivary gland. A pilot study testing NH004 in PD patients has suggested a potentially useful sialorrhea-reducing effect with NH004 compared to placebo. The advantages of NH004 include local bioavailability with low systemic exposure, rapid onset of action and, importantly, convenience of use for patients. This review summarizes the current knowledge and impact of sialorrhea as a common non-motor symptom in PD, treatment options, the anticholinergic drug tropicamide, the design and development of the thin film drug delivery system, and NH004 for the treatment of sialorrhea.

Keywords: Anticholinergics, Clinical study, Drooling, Drug delivery, Parkinson's, Sialorrhea, Thin strips, Tropicamide.

THERAPEUTIC NEEDS IN PARKINSON'S AND OTHER MOVEMENT DISORDERS

Parkinson's disease (PD) is a common neurodegenerative disease present in 1% of the population over 60 years of age, with many motor and non-motor difficulties [1]. There is an increased understanding of the environmental and genetic factors that underlie the loss of nigral dopaminergic neurons and the mechanisms of cell death that contribute to this neuronal loss in PD. Ageing is the single most important risk factor for Parkinson's disease [2]. The salient features in PD are motor tremors, rigidity, bradykinesia and postural instability, all related to loss of the dopamine producing neurons in the substantia nigra area in the brain. Dopamine replacement strategies, notably levodopa, have been the main treatment for almost 40 years and have significantly improved the quality of life for PD patients [3]. Dopamine replacement therapy compensates for the dopamine neuronal loss and reduces motor symptoms in PD patients, but does not stop or slow the neurodegenerative process. Available PD drug therapies are dominated by symptomatic treatments targeting the impairment in motor symptoms.

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In addition, there are several declining non-motor symptoms in PD including cognition, autonomic dysfunction, sleep disorders, dysphagia and drooling. These non-motor symptoms are now well recognized as essential features of PD and increasingly recognized for their impact on a patient's quality of life [4,5]. For example, one study surveyed more than 1000 patients with PD in different stages of their disease and found that overall 98% of the patients reported the presence of one or several such non-motor symptoms [6]. Indeed, these non-motor symptoms can become more important than the motor deficit in influencing the quality of life in the later stages of PD [7]. Many of these symptoms in PD and in other movement disorders are not helped by dopaminergic pharmacotherapies. Research is now being directed at drug therapies to alleviate these symptoms as well.

GASTROINTESTINAL SYMPTOMS AND SIALORRHEA IN PD

Gastrointestinal (GI) symptoms related to PD are recognized as important, yet under-reported, and significantly contribute to disease related quality of life among PD patients [8].

GI symptoms were recognized in PD by James Parkinson in his original 1817 treatise where he clearly identified many of the features of PD recognized today, including sialorrhea. He described drooling *"... the saliva fails of being directed*

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to the back part of the fauces, and hence it is continually draining from the mouth…" [9]. Studies of GI dysfunction in PD [10-15] have found that drooling, dysphagia, nausea and defecatory dysfunction are indeed present more often in individuals with PD than in controls. They found that the frequency of these GI symptoms correlate with the duration and severity of PD and not with diet, activity or treatment, supporting the concept that these GI symptoms are a direct consequence of disease progression. Swallowing problems are increasingly recognized in the PD population. They have a significant impact on Quality of Life and they may lead to drug non-compliance and compromise pharmacological treatment [16,5,8].

Hypersalivation was not identified as a major contributing cause of sialorrhea in PD patients, rather sialorrhea in these patients results from the consequence of less frequent and inefficient swallowing [17,18]. Involuntary drooling of saliva is caused by multiple factors, of which unintended mouth opening and reduced swallowing capacity have been reported to be the most important factors [19]. Additional factors in PD patients include disease severity, stooped posture and reduced ability to be attentive to the need to swallow during activities. Kalf [20] notes that this may explain why drooling is only observed clinically in patients with severe or profuse drooling, while others mainly drool at home where they are unobserved. Perez-Lloret [21] found that saliva volume measurements did not correlate with PD patients' complaints of sialorrhea symptoms.

Consequences of sialorrhea in PD vary from the practical need of a handkerchief or bib, the emotional consequences, to the very negative impact on social functioning in severe situations [20]. Depending on its degree, drooling can result in psychosocial and medical complications, including impaired speech, feeding difficulties, increased risk of aspiration pneumonia, and skin maceration which can be very painful, similar to a burn, and predisposes to secondary infection [22,23]. Drooling is embarrassing for PD patients and may produce a reluctance to go out in public [24]. In addition to causing discomfort, drooling may generate considerable social handicap, leading to patient isolation in mild and moderate cases, and to frequent choking and aspiration pneumonia in severe cases [24].

Sialorrhea in PD has been further reviewed in [25-27] and the most salient aspects are outlined below.

Prevalence of Sialorrhea in PD

Several studies have found sialorrhea to be a major non-motor complaint in PD. The larger studies are summarized in Table **1**. Many PD patients consider drooling as their worse non-motor PD symptom. While the Unified Parkinson's Disease rating Scale (UPDRS) is frequently used to evaluate disease severity and, as noted below, one question specifically tracks salivation, few physicians pay close attention to these non-motor symptoms and thus patients are usually undertreated.

Eadie [10] analyzed gastrointestinal dysfunction in patients compared to aged-matched controls and found drooling among the common GI problems reported. Edwards' [11] study of GI dysfunction in a large group of patients with PD and a control group, found a similar prevalence. In a second study, Edwards [12] confirmed that sialorrhea is a common and not a temporal condition in PD. Siddiqui [14] examined autonomic dysfunction using a global survey of autonomic symptoms, including frequency and severity, in patients with PD and in a control group, and the analysis showed that increased salivation was the most frequent among GI symptoms reported.

Using the Global Screening Questionnaire, Kalf [28] surveyed PD symptoms in 260 consecutive PD patients who

Table 1. Frequency of reported sialorrhea symptoms in PD patients.

	% Reporting (n)		By PD Disease Severity			Assessment Scale
Study	PD	Controls	Mild	Moderate	Severe	
Eadie (1965)	78% (107)					
Edwards (1991)	70% (98)	6% (50)				UPDRS
Siddiqui (2002)	52.3% (44)	12.5% (24)				
Kalf (2007)	48.6% (216)					
Verbaan (2007)	73% (420)	7% (150)	66%	74%	88%	SCOPA–AUT
Martinez-Martin 2007	41.5% (525)					NMS-Quest
Barone (2009)	31% (1072)					
Perez-Lloret (2011)	37% (419)	-	26%	46%	65%	UPDRS
Muller (2011)	42% (207)	5.7% (205)				UPDRS
Chen (2012)	46% (200)					NMS-Quest
Spica (2013)	57% (107)	(late onset)				NMS-Quest
PatientsLikeMe	55.5% (4071)					

visited two movement disorders outpatient clinics. Of the 216 responders (mean age 66.4 years, duration of PD 6.7 years), 105 patients (48.6%) answered that they suffer from involuntary loss of saliva (drooling).

In a study of 420 PD patients compared to 150 controls, Verbaan [29] found that sialorrhea was reported by 73% of the patients and occurred regularly or often in 22%. They further characterized this response according to the stage of disease using the Hoehn & Yahr (H&Y) score, finding that the presence of excess saliva was reported in 88% in individuals in advanced H&Y stages 4&5.

Martinez-Martin [30] studied the prevalence of non-motor symptoms in 525 PD patients using the self-administered NMSQuest scale. Dribbling was particularly prevalent, being reported by 41.5% of the responders.

The PRIAMO study [6] in Italy assessed the prevalence of non-motor symptoms and the impact on patients' quality of life and found that 98.6% of patients with PD reported the presence of non-motor symptoms: and the common symptoms included drooling of saliva (31%). In this study patients were recruited from out-patient clinics mainly in early stages of disease (low mean score of the UPDRS-part III (mean = 24.2), low median stage of the Hoehn & Yahr scale (2), and the relative short mean disease duration of 5.1 years).

Increased saliva is also noted by 42% of persons with newly diagnosed, untreated PD [31].

Two clinical studies (n=200) carried out in China on non-movement disorders in PD patients found an incidence of dribbling of 46% [32].

A study in over 400 PD patients analyzing the prevalence of non-motor symptoms in PD found the prevalence of sialorrhea in 37% of individuals with moderate PD, increasing to 65% in those patients with the highest Hoehn & Yahr scores [33]. Hoehn & Yahr stage was associated with increased saliva or drooling.

In a survey of non-motor symptoms in PD, Spica [34] found drooling in 57% (n=107) of late-onset (onset $\geq$ age 55) PD patients and in 28.7% (n=101) of early onset (between ages 21-45) PD patients.

Websites such as PatientsLikeMe provide an open forum for internet competent patients to network and report their disease symptoms. In over 4000 responses from PD patients of all stages registered on PatientsLikeMe, over 55% reporting excess saliva symptoms [35].

In summary, systematic reviews showed that drooling of saliva is present in more than half of PD patients, ranging from approximately one-third in intermediate stages up to 88% in advanced stages. A meta-analysis showed that the prevalence estimate in PD patients is 56%, with rates depending on the definition [26].

Sialorrhea also has a negative impact on quality of life, especially in advanced PD. Several studies have documented a diminished quality of life.

Among 63 patient respondents with confirmed drooling, 27% experienced severe saliva loss. Social and emotional consequences were reported by 17% to 77% of patients, and significantly more often by those with severe drooling. The authors conclude that drooling is a frequent, disabling and apparently undertreated symptom of PD [28].

Politis [36] investigated the prevalence of the most troublesome motor and non-motor symptoms in PD as perceived by patients by asking 173 advanced PD patients (greater than 6 years disease duration) to rank the top most troublesome symptoms and/or conditions that have affected their quality of life. The top three most prevalent complaints were ineffective medication response, problems with mood and drooling (scoring 115, 96, and 85 points, respectively). While drooling was classified as the third most troublesome symptom, and although PD patients do not particularly associate this symptom with their parkinsonian condition, they nonetheless reported it as the most embarrassing situation that they have to endure resulting in social isolation.

Leibner [37] studied the impact of, and the factors associated with, drooling in PD and found that droolers had worse quality of life and had more difficulty speaking, eating and interacting socially compared to PD non-droolers.

In addition to Parkinson's, sialorrhea is also one of the major non-motor complaints by patients suffering from various neurological impairments, including cerebral palsy, amyotrophic lateral sclerosis (ALS, often referred to in the USA as Lou Gehrig's disease), Huntington's, stroke and traumatic brain injury. Sialorrhea affects up to 37% of patients with cerebral palsy, the US prevalence of which is estimated at 500,000, and approximately 10% required intervention. Other conditions with drooling include Down's and Rett's Syndromes. Other large target populations include millions of survivors of stroke, hemaparesis and severe traumatic brain injury. Sialorrhea may affect up to a million patients with diverse neurological diseases.

Assessment Scales in Clinical Practice

Sialorrhea is frequently assessed by means of rating scales. The Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used rating scale to follow the longitudinal course of Parkinson's disease and in clinical studies. The UPDRS is comprised of five sections that assess limitations of daily activities and non-motor symptoms. Part II 'Activities of Daily Living' section includes questions about speech, salivation, swallowing, handwriting, dressing, hygiene, falling, turning in bed, walking and cutting food. Item 6 of the UPDRS Activities of Daily Living (Part II) specifically tracks salivation:

Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

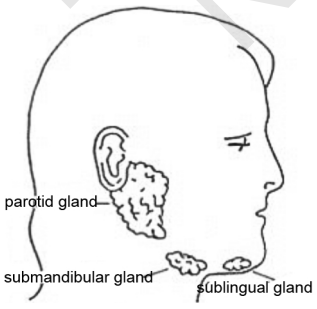
Several PD specific and validated instruments are available for the screening and evaluation of dysphagia and drool-

ing. These include: the Swallowing Disturbance Questionnaire (SDQ); Sialorrhea Clinical Scale for Parkinson's disease (SCS-PD) [21]; Radboud Oral Motor Inventory for Parkinson's Disease (ROMP); and scales with subsections for swallowing and saliva, and non-motor questionnaires that include items on dysphagia and drooling including, Scales for Outcomes in Parkinson's disease- Autonomic (SCOPA-AUT); Non-motor Symptoms Questionnaire for Parkinson's disease (PD-NMSQuest); and Non-motor Symptoms Assessment Scale for Parkinson's disease (NMSS) [20].

The SCS-PD is the only scale developed specifically for the assessment of sialorrhea in PD [21]. It is comprised of 7 0-3 Likert-type items, which aims at measuring sialorrhea-related discomfort. In the validation study it showed good internal consistency and validity, thus suggesting that it might be an ideal tool for sialorrhea evaluation in clinical practice.

Salivary Glands

Three pairs of salivary glands produce saliva which is sent to the oral cavity by way of ducts that open to the inner surfaces of the mouth. One pair of salivary glands, the parotid glands, lie at the side of the face immediately below and in front of the ears; and a second pair, the submandibular glands (also known as the submaxillary glands), lie beneath the tongue and a third pair, the sublingual glands, lie beneath the floor of the oral cavity (Fig. **1**). When an individual is faced with food stimulation, the parotid gland quickly secretes large amounts of saliva. However, in the resting state, the submandibular glands make a greater contribution to the resting whole mouth saliva that coats the oral surfaces for most of the day and night between episodes of stronger stimulation. In this resting state about two-thirds of the saliva in the oral cavity is produced by the submandibular gland, whereas in the stimulated state 70% of the saliva is produced by the parotid glands [38]. You can usually feel the submandibular gland, as it is in the superficial cervical region and feels like a rounded ball. It is located about two fingers above the Adam's apple and about two inches apart under the chin. Humans typically secrete more than a liter of saliva each day, the major portion coming from the parotid and submandibular glands. Saliva is important in beginning the process of digestion and also serves a major role in lubrication, permitting the initiation of swallowing, protecting the mucosal surfaces of the oral cavity from desiccation, and immunity [39].



The salivary glands are innervated by both the parasympathetic and the sympathetic arms of the autonomic nervous system which exert control over salivary gland secretion. Parasympathetic innervation to the salivary glands is carried via cranial nerves. The parotid gland receives its parasympathetic input from the glossopharyngeal nerve (CN IX) via the otic ganglion, while the submandibular and sublingual glands receive their parasympathetic input from the facial nerve (CN VII) via the submandibular ganglion. Direct sympathetic innervation of the salivary glands takes place via preganglionic nerves in the thoracic segments T1-T3 which synapse in the superior cervical ganglion with postganglionic neurons that release norepinephrine [40].

Salivary gland secretion is mediated through muscarinic acetylcholine receptors (mAChRs). These mAChRs regulate the activity of numerous central and peripheral nervous system functions. The mAChRs belong to a large superfamily of G protein-linked integral member protein receptors with seven transmembrane segments. Acetylcholine binds to mAChRs, thereby activating intracellular GTP-binding regulatory proteins (G proteins). There are five mAChRs designated M1-M5: subtypes M1, M3, M5 define one class and interact with Gq-type G proteins; subtypes M2, M4 define a second class and interact with Gi/Go-type G proteins. Activated G proteins then initiate a number of intracellular signal transduction systems. Agonist-bound muscarinic receptors are phosphorylated by G protein-coupled receptor kinases, which initiate their desensitization through uncoupling from G proteins, receptor internalization, and receptor breakdown. The five molecularly distinct mAChR (M1-M5) have been cloned and characterized [41].

While salivary secretion has been shown to be mediated mainly through M3 and, to a lesser extent, M1 muscarinic cholinergic receptors, several studies indicate a role for other receptor subtypes, both pre- and post-synaptically, in mediating fluid secretion in the salivary glands [40]. The relative roles of the muscarinic acetylcholine receptors in salivary secretion vary by species (rodent, ovine and human) and salivary gland (parotid, submandibular) [42]. Given this variation, it is important to note that much of the understanding of salivary secretion is based on the frequently employed rat parotid gland animal model. There has been a widespread acceptance, based on studies of this model, that salivary secretion is mediated entirely by M3 receptors. However, results indicate a role for M1 receptors, in addition to M3 receptors, in mediating salivary fluid secretion and a possible role for M4 receptors in regulating salivary protein secretion [43]. Tobin and others indicate that secretion by the rabbit and rat submandibular and rat sublingual salivary glands is also partially mediated by M1 and other non-M3 receptors [40,43].

TREATMENTS FOR SIALORRHEA

The goal of treatment for sialorrhea is to reduce drooling but maintain a moist, healthy oral cavity. To completely eliminate drooling risks the significant complication of xerostomia (dry mouth). In a study of the effects of anticholinergic agents on salivary flow, the subjects experienced the sensation of dry mouth when the normal flow rate of unstimulated saliva was reduced by from 40 to 50% [103].

The management of sialorrhea in PD patients has been summarized in frequent reviews [45,20,46,47,48,23] attesting to the interest of medical practitioners and the concern of

their patients. The Movement Disorder Society (MDS) has a task force on evidence based medicine (MDS-EBM) which periodically reviews treatments for PD. Early MDS-EBM reviews focused on treatments for motor symptoms, however in the most recent review [49] the task force decided it was necessary to extend the review to non-motor symptoms, including sialorrhea. The reviewed evidence suggested that Botulinum toxin A or B were 'clinically useful' for the treatment of sialorrhea in PD, whereas glycopyrrolate was 'possible useful', as it showed efficacy only in the short-term. In this section the salient characteristics of some treatments will be reviewed.

Numerous therapeutic approaches have been attempted to treat sialorrhea in PD patients, but all of them have limitations. Current approaches include surgical procedures (irreversible, invasive), prosthetic devices (not practical, uncomfortable), intrasalivary gland botulinum toxin injections (wears off in a few months), systemic anticholinergic drugs (undesirable side effects), and speech and behavioral therapy (not shown to be effective in controlled trials). Chewing gum or sucking on hard candy in social situations makes swallowing a more conscious action, thus reducing drooling despite actually increasing saliva production [50]. As a result of the limitations of the current treatment approaches, PD patients often use handkerchiefs and bibs to cope with sialorrhea. No single therapy has been documented to resolve sialorrhea satisfactorily in all patients. Rather, a combination of therapies is often required.

The several drug approaches for the treatment of sialorrhea can be categorized as (1) botulinum toxins, (2) anticholinergic drugs, comprising both tertiary or quaternary amines, and (3) drugs with other mechanisms of action.

Botulinum neurotoxins type A and B, given as intraglandular injections, have been shown to be clinically useful as a treatment for sialorrhea. Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and thereby decreasing the release of acetylcholine, causing a neuromuscular blocking effect. Botulinum neurotoxins are synthesized as a single chain (150 kD) and then cleaved to form a two chain molecule with a disulfide bridge The light chain (~50 kD) acts as a zinc endopeptidase, similar to tetanus toxin, with proteolytic activity located at the N-terminal end. The heavy chain (~100 kD) provides cholinergic specificity and is responsible for binding the toxin to presynaptic receptors. Botulinum toxin type A cleaves synaptosome-associated protein (SNAP-25), a presynaptic membrane protein required for fusion of neurotransmitter-containing vesicles whereas botulinum toxin B cleaves a vesicle-associated membrane protein (VAMP), also known as synaptobrevin.

Injections of botulinum toxins of various doses into the salivary glands can reduce saliva production for several months. The safety is deemed acceptable with specialized monitoring. A recent comprehensive review [51] of treatment options for sialorrhea due to various neurological conditions, with an emphasis on the role of botulinum neurotoxins, concludes that the administration of botulinum toxins into salivary glands is currently the most effective way of treating sialorrhea, although several technical details are yet to be optimized.

The neurotransmitter acetylcholine binds to and activates acetylcholine receptors (AChR). Anticholinergic drugs bind to but do not activate these receptors, thereby blocking the effects of endogenous acetylcholine and other cholinomimetics at cholinergic receptors on effector cells. Anticholinergic drugs fall into two major families: (1) anti-nicotinic drugs which include ganglion blockers (ex.: bupropion, hexamethonium, dextromethorphan) and neuromuscular blockers (ex: gallamine, tubocurarine, pancuronium) and (2) antimuscarinic drugs which include tertiary amines (atropine, scopolamine, tropicamide), and quaternary amines (propantheline, ipratropium, benztropine). Antimuscarinic agents operate on the muscarinic acetylcholine receptors.

Muscarinic antagonists have widespread effects including actions on the iris and ciliary muscle of the eye, the heart and blood vessels, secretions of the respiratory tract, GI system, and salivary glands, GI motility, urinary bladder tone, and the central nervous system. The number of muscarinic receptor antagonist drugs producing xerostomia (dry mouth) as a side effect is extensive. Anticholinergic muscarinics have been shown to be effective in reducing saliva secretions and in alleviating the symptoms of sialorrhea. However, the currently available muscarinic antagonists (i.e., glycopyrrolate, scopolamine, atropine, benztropine, trihexyphenidyl) involve systemic administration that results in adverse side effects such as constipation, urinary retention, blurred vision, restlessness, memory impairment and xerostomia (dry mouth), which limit their potential. See [52,53] for a fuller description of antimuscarinic drugs.

Glycopyrrolate is a non selective anti-muscarinic drug approved to treat ulcers. It has been shown to be effective in the control of excessive sialorrhea in children with developmental disabilities, however approximately 20% of the treated individuals experienced substantial adverse systemic side effects requiring discontinuation of medication [54]. Others studies employing systemic administration of glycopyrrolate have reported behavioral changes.

Arbouw [55] conducted a four-week, randomized, double-blind, placebo-controlled, crossover trial with oral glycopyrrolate 1 mg administered twice daily in 23 patients with PD and found the treatment to be effective and safe. Glycopyrrolate oral solution is the only approved product (Cuvposa®, Merz Pharmaceuticals) to reduce chronic severe drooling. It is a liquid formulation available in pediatric doses that must be measured and administered with an accurate measuring device taken three times daily in children with problem drooling, such as cerebral palsy [56].

The use of atropine sulfate tablets to treat sialorrhea has been reported [57]. Side effects include mild stimulation to the central nervous system at low doses, while larger doses can cause mental disturbances, depression and worsening of constipation. Death from atropine poisoning, though rare, is usually due to paralysis of the medullary centers.

Given that systemic atropine is often poorly tolerated by elderly patients with PD, Hyson [58] conducted a study with six PD patients complaining of drooling by administering a sublingual atropine solution twice daily. It was concluded that this appears to be useful to treat sialorrhea, however, anticholinergic side effects (hallucinations) were docu-

mented. No effect was noted after 30 minutes and results were first observed three hours after the initial treatment.

Ipratropium is structurally related to atropine but whereas atropine is a neutral tertiary amine, ipratropium is a charged quaternary amine. Other investigators [59,60] have similarly reported the use of ipratropium bromide at bedtime for the treatment of clozapine-induced sialorrhea in patients diagnosed with schizophrenia. In one case [59] patients used the drug intra-nasally and within 1-2 weeks, 6 of 10 patients reported mild to moderate improvement and 2 patients reported a significant improvement. In a different study [60] patients used ipratropium sublingually and most patients had a partial yet clinically meaningful response. However, in another PD study [61], ipratropium spray was found to be ineffective in an objective measure of saliva production but may have had a mild effect on subjective sialorrhea measure in a double-blind, randomized, crossover trial.

Other pharmacological treatments have been proposed to treat sialorrhea including the use of amitriptyline (a tricyclic antidepressant) and clonidine (an alpha-2-selective adrenergic agonist). Salivary glands receive sympathetic in addition to muscarinic innervation, and while the muscarinic is the more important system, activation of either system is known to increase secretion.

Clonidine is an imidazole-type an alpha-2 selective adrenoreceptor agonist primarily used clinically as an antihypertensive agent. It acts in the CNS to reduce sympathetic nervous tone to the periphery. It stimulates alpha2 adrenoceptors in the brain and causes sedation side-effects and dry mouth. In some open case series, clonidine has shown encouraging results in reducing sialorrhea induced by the antipsychotic drug clozapine [62,63]. In another study, the efficacy of clonidine was compared to placebo in PD patients, and the group treated with clonidine showed a significant reduction of drooling. However, of the 17 patients receiving drug, four experienced side effects [64].

Another approach that has been tried is combination therapy using the anti-muscarinic oxybutynin and alpha-2 adrenergic agonist clonidine. Oral administration of a combination of these two off-patent drugs has been tested to treat sialorrhea (ClinicalTrials.gov Identifier NCT01370811) [65].

While these systemic drugs have been shown to decrease the amount of saliva production, they have side-effects. Of particular concern is the effect of systemic anticholinergics on cognition impairment in PD patients. The goal of treatment is to reduce drooling but maintain a moist, healthy oral cavity. No single therapy has been documented to resolve sialorrhea satisfactorily in all patients. If antimuscarinics are to be used for reducing saliva production, it is important that side effects from a potential medication are considered in light of the overall quality of life improvement.

Tropicamide - New Use to Treat Sialorrhea

The ideal treatment would be an anti-sialorrhea effect (reduced saliva secretion) that acts locally to maximize efficacy and limit systemic side effects. The goal is to neither completely reduce saliva secretion nor to prevent saliva production in response to food, since saliva is needed for proper ingestion. The sensation of oral dryness may occur when a person's normal unstimulated flow rate is reduced by about 50% [66]. Blasco [67] points out that drooling in cerebral palsy patients varies considerably from day to day and during the day so that control is a constantly changing need. Therefore patients would like to be able to control the specific time that they obtain relief from sialorrhea. The attributes of an ideal product to treat sialorrhea are a) fast onset of relief, b) duration of a few hours, c) convenient, "as needed" inconspicuous method of delivery, and d) good safety profile.

Antimuscarinic drugs have different physical and pharmacologic properties. Many anticholinergics are used in ophthalmology to block the receptors in the muscles of the eye for mydriasis (dilation of the pupil) and for cycloplegia (paralysis of the ciliary muscle of the eye, resulting in a loss of accommodation of near vision) so that eye examinations can be carried out thoroughly. The pharmacokinetics of tropicamide as compared to the other anticholinergics suggest that it might be a good choice for sialorrhea treatment. As measured by ophthalmic response kinetics, tropicamide has the fastest onset and shortest duration of action compared with these other antimuscarinic agents. Due to its lower pKa, it has a higher corneal penetration. Some anticholinergic drugs used in ophthalmic applications are listed in Table **2** along with their time to maximum effect and duration of action [68,69]. Atropine, scopolamine and homatropine are known to have systemic side effects; and tropicamide is considered safer than cyclopentolate [69].

Vuori [70] studied the relative binding of atropine and tropicamide to muscarinic receptors in plasma. The IC_{50} for tropicamide was 1150 ng/ml and for atropine 3.8 ng/ml, thus atropine was about 300 times more potent than tropicamide for muscarinic receptors in plasma. Based on the Ki values, the concentration of tropicamide required for half-maximal muscarinic receptor occupancy was 60 ng/ml and about 0.2 ng/ml for atropine. Due to this difference in binding affinity, atropine completely saturates receptor sites at ng/ml concentrations, whereas tropicamide requires ug/ml concentrations. The authors conclude that this difference in binding affinity and muscarinic receptor saturation between these two drugs is probably responsible for the difference in ocular and systemic effects.

Tropicamide has been widely and safely used in ophthalmology for humans and animals for over 50 years. Tropicamide was first approved by the FDA in 1960 (Mydriacyl, Alcon Labs) and currently approved as an aid in ophthalmic diagnosis and procedures [71,52]. It is used in liquid form as topically applied eye drops to produce mydriasis and cycloplegia for ophthalmic purposes. It is available only to ophthalmologists by prescription. The dose in ophthalmic use ranges from 0.5 to 2.5 mg of tropicamide per eye (1 to 5 mg total). Single doses of tropicamide in this range have been studied as a possible therapy for sialorrhea.

Overall, the advantages of tropicamide over other known anti-muscarinic drugs for the treatment of sialorrhea are based on the pharmacology, quick acting and short duration pharmacokinetics, and extensive safety profile of the drug. Additional advantages, based on the route and means of administration, are described below.

Table 2. Properties of anti-cholinergic drugs used in ophthalmology.

		Time to Maximal Effect		Duration of Action	
	pKa	**Mydriasis**	**Cyclopegia**	**Mydriasis**	**Cyclopegia**
Atropine	9.8	30-40 min	1 day	7-10 days	2 weeks
Homatropine	9.9	30-60 min	30-60 min	1-2 days	1-3 days
Scopolamine (Hyoscine)	7.7	40 min	40 min	6 days	7 days
Cyclopentolate	8.4	15-30 min	15-30 min	24 hrs	24 hours
Tropicamide	5.4	15-30 min	25 min	4-6 hrs	6 hours

Exploratory Studies with Tropicamide to Treat Sialorrhea

Exploratory studies testing the effect of tropicamide in solution administered intra-orally to treat sialorrhea in Parkinson's patients were performed at the movement disorders section of the FLENI Institute [102].

In one small group of PD patients complaining of sialorrhea, a single dose of tropicamide (20 drops of 1% solution, 10 mg tropicamide total) was administered in the mouth and kept in the mouth without swallowing for 10 minutes. The aim was to assess personal impression by the patients of their sialorrhea symptoms, including, drooling, speech performance, and social interference, as well as the presence of side effects, such as blurred vision, confusion, somnolence, tachycardia, hypotension, or any other discomforting sensation. Patients rated themselves on a visual analog scale as to the disability incurred by their sialorrhea both before and one hour after the treatment. In addition, they were asked about the latency of the effect. The results indicated that all patients improved after the administration of the tropicamide drops. The average improvement was 48 ± 33% (range 10% - 90%). Latency to the onset of the effect was within 30 ± 8 minutes post-administration. A quantitative assay was used to follow the time course of saliva production in one treated patient. The results demonstrated that a significant effect occurred relatively rapidly and lasted up to 1.5 hours.

A further group of Parkinson's patients suffering from sialorrhea tested a 1% tropicamide solution similarly applied to their tongues on an 'as needed' basis to treat their excessive salivation. Some patients reported that the treatment was useful and continued to use the tropicamide drops over a period of months.

These studies suggested that tropicamide could pharmacologically provide the needed relief, however a more suitable, convenient and controllable dosage and delivery means is necessary.

DRUG DELIVERY - TROPICAMIDE FORMULATED IN THIN FILMS

Intra-oral administered formulations of tropicamide can rapidly provide an effective amount of the anti-cholinergic drug agent into the oral cavity for absorption across the mucosal epithelium to the underlying salivary gland(s). Local administration of tropicamide avoids or minimizes the undesirable side effects of anticholinergics given systemically. The remaining technical issue was to find a convenient drug delivery means. Orally dissolvable thin-strip delivery form, as modified, fits the desired product profile well.

Thin strip (or "thin film") delivery means has been increasingly used as a convenient formulation to provide oral administration of drugs without the need for water to help swallow a pill. Postage stamp size, flexible, thin strip films can be placed in the mouth (buccally or sublingually) where the film dissolves, usually in a few seconds, releasing the drug into the oral cavity. Films are prepared using hydrophilic polymers that dissolve on contact. Various types of rapidly dissolving (quick-dissolving) intra-orally administrable film compositions have been described [72,73,74].

Oral dissolving film (ODF) drug delivery has emerged as an advanced alternative to tablets, capsules and liquids. There are many commercial non-drug products using thin film delivery including Listerine PocketPaks® breath freshening strips and Meltz Super Thin Mints. Thin film technology is used in a number of over-the-counter cold, flu, anti-snoring and gastrointestinal medications [75]. The U.S. FDA has also approved several ethical products using thin strip technology including Zuplenz (ondansetron for chemotherapy-induced nausea), Suboxone® (buprenorphine and naloxone combination product for opioid addiction), and Onsolis® (fentanyl for the management of pain) [76] and others under development [77].

Based on the release kinetics and desired residence time of the anti-cholinergic agent in the mouth, the disintegration time and the dissolution time of the thin strip can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. The delivery system can be prepared with zero order kinetic release of the contents or with first order kinetic release of the contents (e.g., 50% of the drug can be release within the first few minutes and the remaining over a longer time period). The disintegration rate (rate at which a composition falls apart) and the dissolution rate (rate of appearance of anti-cholinergic agent from a composition) are parameters of film compositions that are known to be a function of the relative amounts of hydrophobic excipients present in the composition. As the relative content of hydrophobic excipients rises compared to other ingredients, the slower the film composition will disintegrate and dissolve [72].

In addition, thin films can be formulated with a muco-adhering agent so that the film can be placed at and adhere to a preferred location in the mouth (i.e., near the salivary

glands) and not subsequently float to another location. Consequently the film is not swallowed, but will reside exclusively in the mouth where it dissolves upon contact with saliva or mucosal surface to release an effective amount of the drug for absorption across the mucosal epithelium to the underlying local salivary glands [73].

The film compositions may also comprise other excipients to improve the organoleptic properties (smell, taste, texture, feel) of the film composition when placed in the oral cavity. A film composition is perceived to "melt" in the mouth and leave a smooth pleasant feel and taste following dissolution. A variety of pharmaceutically acceptable excipients may be employed to provide such desirable features to improve utility of the film compositions. Films may also vary in size, e.g., from 1 to 5 cm^2, depending on the desired placement in the oral cavity.

NH004 - Tropicamide Thin Film Design

As mentioned earlier, for sialorrhea control, it would be desirable to have an anticholinergic drug released slowly from a thin film over time and to provide local delivery to the underlying salivary glands. In addition, since patients with movement disorders would have a difficult time maintaining the thin strip in the oral cavity for any length of time, having the thin strip adhere to the buccal surface near the targeted salivary gland would also be a desirable property.

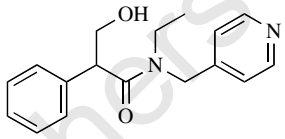
NH004 is a slow orally dissolving film being developed for the local delivery of tropicamide to control the symptoms of sialorrhea in patients suffering from Parkinson's disease and other motor disorders. NH004 contains tropicamide formulated in a novel and convenient drug delivery means known as thin films or "thin strips." It is modeled on Listerine PocketPaks® breath strips, with two significant modifications: (1) The film used in NH004 is formulated with a muco-adhesive property which makes it adhere to any buccal surface and allows placement near the submandibular salivary glands to maximize the local drug action while minimizing systemic absorption. Tropicamide is absorbed across the mucosal epithelium of the mouth to reduce saliva production from the underlying salivary glands. (2) After placement in the mouth, the NH004 film dissolves slowly over a 30-60 minute period, releasing the active pharmaceutical ingredient tropicamide into the oral mucosa. It is released without mastication or the need for intake of water. All excipients are USP, NF or equivalent. Stability for two years has been demonstrated.

NH004 begins to act quickly and its effect last for approximately 2 hours, making it ideal for use on an "as needed" basis when the individual most desires to alleviate his/her condition, for example during a social situation or in-between meals. NH004 films can be applied on a single side or bilaterally, depending on the magnitude of the desired effect. Patients find NH004 features very appealing because it can be used inconspicuously and others would not be aware it is a medicine, a real advantage for an embarrassing condition. Another attractive feature of NH004 films is the ability to readily modify the amount of the drug and excipients (such as flavors) or change the dissolution rate, and thereby differentiate a spectrum of products.

TROPICAMIDE - CHEMICAL AND PHYSICAL PROPERTIES

The active pharmaceutical ingredient in NH004 is tropicamide (N-ethyl-alpha-(hydroxymethyl)-N-(4-pyridinylmethyl)-benzeneacetamide), CAS 1508-75-4.

Chemical structure of tropicamide ($C_{17}H_{20}N_2O_2$), mol wt 284 kDa:



Tropicamide is a tropic acid derivative chemically synthesized by reacting O-acetyltropyl chloride with ethyl (4-pyridinylmethyl)amine and the subsequent acidic hydrolysis of the acetyl group in the resulting amide [78]. While the compound described here is the racemate, stereospecific synthetic pathways have also been described [79]. Relevant physical properties of tropicamide include fusion point of 95-98 °C, pKa 5.2-5.4 (essentially 100% unionized at pH 7.4) and soluble in DMSO to 100 mM and in ethanol to 20 mM.

Mechanism of Action

Tropicamide is a synthetic tertiary amine anticholinergic agent that blocks acetylcholine muscarinic receptors and prevents acetylcholine from activating these receptors. It is well established that salivary fluid secretion is largely dependent on acetylcholine acting on muscarinic receptors. For sialorrhea control, tropicamide acts by blocking the muscarinic acetylcholine receptors of the salivary glands. As a short-acting anticholinergic agent, tropicamide (plasma half-life of 30 min) has the potential to reduce saliva secretion without the side effects associated with long-acting cholinergic blockers.

There are discrepancies reported in the mAChR subtype specificity of tropicamide. Tropicamide is often cited as an antagonist with moderate binding selectivity for M4 AChR. As observed in Table **3**, the drug blocks all subtypes of muscarinic receptors, and not just M4 receptors as was initially suggested [80]. Notwithstanding, a small degree of M4 selectivity for tropicamide was observed in further experiments [81,82].

However this tropicamide specificity has not been confirmed by other experiments on mAChR subtypes [83,84]. Dong [84] found that tropicamide showed the highest affinity for the M2 subtype and then for the M4, M5, M1 and M3 subtypes, in this order. Furthermore, Dei [79] show results that the tropicamide enantiomers are not able to significantly discriminate among M1-M4 receptors and therefore do not support the proposal of tropicamide as an M4 selective agent.

Non-Clinical Toxicology - Single and Repeat-Dose

After acute oral administration of tropicamide, the LD_{50} value in mice is 565 mg/kg and 865 mg/kg in rats (> 10^4 higher than NH004 dose for sialorrhea control). The current dose of tropicamide for topical ophthalmic use ranges from 1-5 mg (equivalent to <0.1 mg/kg). Tropicamide lethal doses 50% (LD_{50}) are shown in Table **4** [86].

Table 3. Binding constants of tropicamide to human mAChRs (pKb).

	Ref	Receptor M1	Receptor M2	Receptor M3	Receptor M4
Tropicamide	[80]	7.18 ± 0.04	7.30 ± 0.05	7.42 ± 0.05	nd
Tropicamide	[81]	7.27 ± 0.03	7.34 ± 0.04	7.30 ± 0.05	7.82 ± 0.10
Tropicamide	[83]	7.80 ± 0.11	6.84 ± 0.08	6.92 ± 0.16	7.26 ± 0.06
Tropicamide	[84]	6.98 ± 0.03	7.62 ± 0.03	6.95 ± 0.18	7.55 ± 0.29
S-Tropicamide	[79]	7.28 ± 0.11	7.50 ± 0.09	7.18 ± 0.12	7.81 ± 0.10
Atropine	[85]	9.0	8.7	9.2	8.9

For comparison, the binding affinities for atropine are indicated [85].

Table 4. Tropicamide acute LD_{50} values.

Route / Species	LD_{50}
Intraperitoneal / Mice	695 mg/kg
Intraperitoneal / Rats	1,210 mg/kg
Oral / Mice	565 mg/kg
Oral / Rats	865 mg/kg
Subcutaneous / Mice	665 mg/kg
Subcutaneous / Rats	872 mg/kg

Repeat toxicology studies of tropicamide as an ophthalmic solution have also been reported. A chronic toxicity study was carried out in rabbits and dogs, by instilling ascending doses of tropicamide into one eye for a period of twelve weeks, with the untreated eye serving as control [87]. Gross and microscopic examination of the kidney, liver, spleen and the eye revealed no pathology even in concentrations five times that which is used clinically. As reported by Gettes [88], prolonged topical application of tropicamide eye drops in animals found no evidence of any injury, acquired sensitivity, or allergic reaction to the eye. In an ocular irritation test, rabbits received 5 ocular instillations of 1% tropicamide solution five times daily for 5 days. Draize scores revealed no evidence of irritation or toxicity (Alcon NDA 1970).

Therefore, it can be concluded that single and repeated dose studies with tropicamide support its clinical use.

Clinical Experience with Tropicamide

Tropicamide has been available for human use for more than 50 years in an ocular formulation. For eye refractions, one or two drops of a 1% solution (i.e., 0.5 – 1 mg) are dispensed in each eye, repeated in five minutes. If the patient is not seen within 20 to 30 minutes, an additional drop may be dispensed to prolong the mydriatic effect. Therefore, doses can reach 5 mg of tropicamide. Millions of patients have been exposed to tropicamide to date, thus providing a great deal of clinical experience to support its safety. Two reports observed no adverse events after tropicamide 1% ocular solution instillation in over 10,000 treated patients [89] and in over 1,000 treated patients [90].

Complications from the use of tropicamide eye drops in humans are rare compared to its long history of extensive use. Rengstorff [69] extensively reviewed and summarized ocular and systemic side effects of commonly used cyclopegic drugs including tropicamide, cyclopentolate, atropine, scopolamine and homatropine; effects noted were related to dosage, concomitant use with other drugs, trauma or in very ill patients . When applied into the eyes, mydriatic drugs such as tropicamide can cause an increase in intraocular pressure, allergies, discomfort or blurred vision. Tropicamide was found to be the safest among these drugs, with rare instances of transient elevated intra-ocular pressure. The only systemic effect noted was drowsiness.

Another large study [91] looked at the incidence of glaucoma in nearly 600,000 people and found that while acute glaucoma occurs in 1 /18,000 patients treated with various antimuscarinic drugs, no instances were observed with tropicamide and concluded that the use of tropicamide alone for mydriasis is safe even in people with chronic glaucoma.

Tropicamide is routinely used for mydriasis in neonates and preterm babies at doses and regimens commonly used for adults: tropicamide concentrations of 0.5% - 0.75% solutions, frequently two to three installations administered over a 5-30 minute time period. This is a 10x exposure on a mg/kg basis.

While tropicamide is frequently administered to elderly and young patients, who are more susceptible to possible side effects of anticholinergics, no overall differences in safety or effectiveness have been observed among these populations [92,71]. Moreover, chronic exposure to tropicamide in children for up to 2 years without any notable side effects has also been reported. Both tropicamide and atropine have been administered daily for prolonged periods to children aiming at preventing myopia [93,94]. For example, 186 children, from 6 to 13 years of age, were treated nightly with three concentrations of atropine eye drops or 0.5% tropicamide for up to 2 years [95]. Similarly, twelve myopic children aged 7-14 were treated with 0.5% tropicamide eye drops once per night for 9-22 months [96]. In two earlier studies, 61 children aged 6–16 years were given daily 0.4% tropicamide eye drops [97] and in a matched pair design of 26 twins in the United States were administered two drops of 1% tropicamide nightly, but showed no significant differences in myopia progression after 3½ years of follow up [98]. In an interesting clinical design to further study

whether myopia can be prevented in children by using a low concentration of atropine eye drops, the control group treatment consists of using 0.5% tropicamide eye drops every day (NCT00541177). While these daily tropicamide treatments did not arrest the progression of myopia in children [99], the experience shows that daily exposure tropicamide is safe in these populations.

As with other anticholinergics, there can be potentiation of the antimuscarinic effect with other anticholinergics (including orphenadrine) and interactions with serotoninergic antidepressants. Tropicamide may interfere with the antihypertensive action of carbachol, pilocarpine, or ophthalmic cholinesterase inhibitors [71]. No interactions with levodopa, dopamine agonists or any other antiparkinsonian drug have been reported.

Tropicamide does not have any known active metabolites. Inhibitory binding assays with tropicamide on several cytochrome P-450 isoforms have revealed an IC50 of 1000 nM for isoforms 2C9 and 2C19, and no activity on isoforms 1A2, 2D6 and 2E1 (DRUGMATRIX toxicology reference database).

Tropicamide Pharmacokinetics and Plasma Receptor Binding

The plasma levels and systemic anticholinergic activity of tropicamide have been studied in healthy adults after ocular topical administration [70]. Two 40 microliter drops of tropicamide (0.5%) were instilled into the lower cul-de-sac of one eye of the subjects, and concentrations and respective muscarinic receptor occupancy of tropicamide in plasma were monitored using radioligand binding techniques. No adverse events were reported.

Results showed rapid absorption of tropicamide from topically applied eye drops into the systemic circulation, and subsequent distribution and elimination of tropicamide from the central blood compartment [70]. Tropicamide was rapidly absorbed systemically with the mean peak concentration in plasma being 2.8 +/- 1.7 ng/ml (mean +/- SD) at five minutes after instillation. Tropicamide disappeared rapidly from the systemic circulation: drug concentration in plasma was 0.46 +/- 0.51 ng/ml (mean +/- SD) at 60 minutes and below 0.24 ng/ml at 120 minutes after instillation.

Binding experiments demonstrated that tropicamide bound to muscarinic receptors of rat brain with an apparent equilibrium binding constant (Ki-value in plasma) of 220 +/- 25 nM (mean +/- SD). Tropicamide occupied maximally 8% of muscarinic receptors in human plasma after ocular application. At the peak drug concentration (five minutes after dosing), the mean fractional receptor occupancy of tropicamide in plasma was only 4%. The authors [70] suggested that the low affinity of tropicamide for muscarinic receptors and its negligible receptor occupancy in human plasma can explain the low incidence of systemic side-effects of tropicamide.

NH004 - TROPICAMIDE CONTAINING THIN FILMS

Comparative Pharmacokinetics

A study comparing the pharmacokinetics of tropicamide administered ocularly, orally or as a mucoadhesive film to rabbits was conducted, along with a microscopic examination of the intraoral tissue [100]. This study assessed the pharmacokinetics and toxicity of tropicamide following a single identical 3.3 mg dose via topical ocular (eye drops), oral (mouth gavage), or intra-oral (muco-adhesive thin film placed inside the mouth) administration to three groups of rabbits. Blood samples were collected over time for plasma analysis and the systemic pharmacokinetics of tropicamide was determined. Two groups were dosed via the topical ocular and oral routes, respectively, with a 1% tropicamide solution, the liquid equivalent of the dose delivered by the intraoral muco-adhesive thin film group. Blood samples were collected before dosing and at 1, 5, 10, 15, 30, and 45 minutes and 1, 1.5, and 2 hours after dosing. Pharmacokinetics of tropicamide as a 1% solution and the mucoadhesive system were determined.

After topical ocular administration, tropicamide was rapidly absorbed with a mean Tmax value of 1.00 minute and readily eliminated from plasma with a $t_{1/2}$ value of 22.2 minutes. The mean C_{max} and $AUC_{0\text{-}120}$ values were 483 ng/mL and 7804 ng•min/mL, respectively.

After oral administration, tropicamide was readily absorbed with a mean Tmax value of 10.3 minutes and readily eliminated from plasma with a $t_{1/2}$ value of 32.4 minutes. The mean Cmax and $AUC_{0\text{-}120}$ values were 136 ng/mL and 3754 ng•min/mL, respectively. The relative bioavailability between oral administration and topical ocular administration was 48.1%.

After intraoral mucoadhesive thin film administration, tropicamide was readily absorbed with a mean Tmax value of 25.0 minutes and readily eliminated from plasma with a $t_{1/2}$ value of 21.9 minutes. The mean Cmax and $AUC_{0\text{-}120}$ values were 107 ng/mL and 4933 ng•min/mL, respectively. The relative bioavailability between intraoral administration and topical ocular administration was 63.2%.

The summary of the pharmacokinetic parameters for tropicamide are presented in Table **5**. Tropicamide was absorbed most rapidly after topical ocular administration with the highest Cmax value and the shortest Tmax value compared to the other routes of administration. Topical ocular administration resulted in the greatest exposure to tropicamide in rabbits. In rabbits, the mean $AUC_{0\text{-}120}$ value after topical ocular administration was markedly (>2.0 fold) higher than after oral administration. The mean concentrations of tropicamide in rabbit plasma are presented graphically in Fig. (**1**).

This study showed that in comparison to the common ocular (eye drops) formulation, the oral or intra-oral formulations of tropicamide resulted in a lower C_{max} and AUC, thus reflecting lower systemic drug absorption. It is also worthwhile to note that the intra-oral thin film formulation provided a more constant levels of tropicamide over time reflecting the slow release of the tropicamide from the film, as in the desirable product profile. The lack of pharmacologically significant differences in plasma half- life may suggest that drug distribution, disposition and elimination remained unchanged among the three tested formulations.

Based on the fact that the systemic exposure, in terms of both the Cmax and AUC were 40% smaller for the NH004

Table 5. Pharmacokinetic parameters for tropicamide by route of administration in rabbit plasma.

Route		C_{max}	T_{max}	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	Treatment Ratios [a]	
		(ng/mL)	(min)	(ng•min/mL)	(ng•min/mL)	(min)	Cmax	$AUC_{0-\infty}$
Topical Ocular	Mean	483	1.00	7712	7804	22.2	NA	NA
	SD	77	0	2173	2184	3.4		
Oral	Mean	136	10.3	3553	3754	32.4	0.281	0.481
	SD	90	8.1	1213	1252	6.3		0.160
Intraoral (film)	Mean	107	25.0	4337	4933	21.9	0.221	0.632
	SD	39	17.3	1197	NA	NA		

[a] The mean AUC(0-∞) value for the topical ocular treatment was used as a reference for relative bioavailability ratios. NA, not applicable.

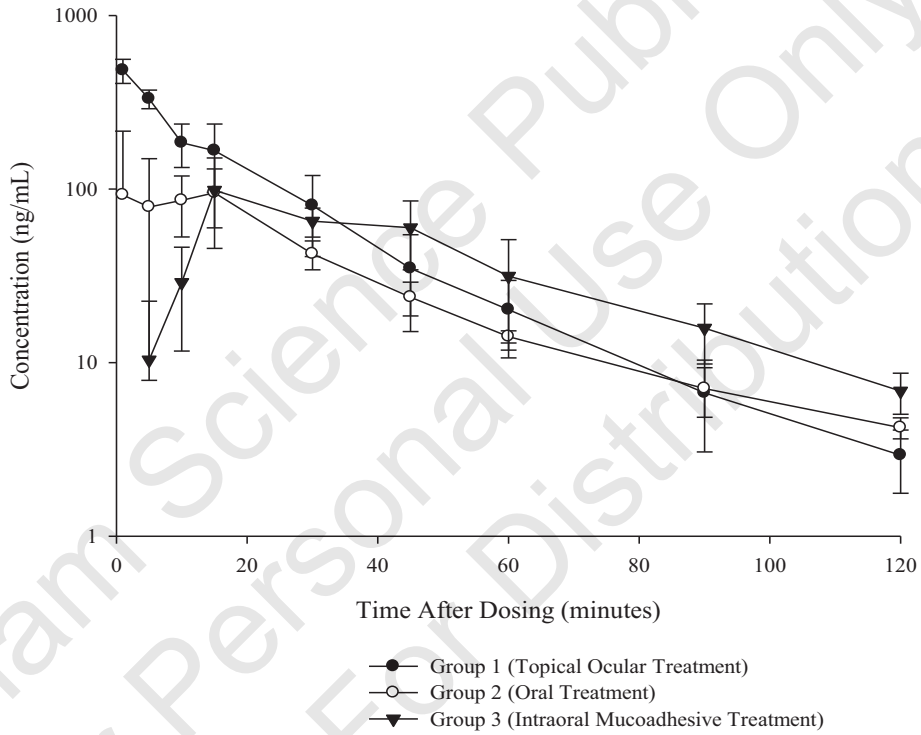


Fig. (1). Concentrations (ng/mL) of tropicamide in plasma as a function of route of administration over time. Means ± standard error of the mean are shown.

films than for ophthalmic administration, strongly suggests that NH004 film administration would be at least as safe as the standard ophthalmic administration of tropicamide.

Safety Pharmacology

In the rabbit study cited above, safety parameters were also assessed. Pupil dilation was also measured in both eyes of each animal once prior to sedation/dosing, immediately after dosing, and just prior to each post-dose blood collection time point. The pre-dose pupil dilation measurements (pupil width) ranged from 4 to 7 mm for all rabbits. Mydriasis was evident, as expected, in the eyes of the rabbits dosed by the topical ocular route beginning at 5 minutes post-dose (6 to 10 mm) and persisting at 10 mm from 10 minutes post-dose through the last measurement at 2 hours post-dose. Results showed that topical ocular administration led to mydriasis as expected, a phenomenon that was not observed after administration of the drug by the oral or intraoral routes.

Drug toxicity was also evaluated. In addition, macroscopic and microscopic evaluations of the cheek tissues in the animal receiving the thin films were conducted. Body weights were collected prior to dosing and prior to scheduled sacrifice after the last blood collection. All animals survived with no clinical signs noted, except for a small laceration on the muzzle skin of one animal that was considered to have been caused by shaving. Body weight decreases noted in all animals were attributed to food fasting after dosing. No signs of toxicity were noted following a single ocular, oral, or intra-oral dose of tropicamide in rabbits.

The reactogenicity of the NH004 muco-adhesive thin strips on the inner mucosal surface of the test animals was determined by biopsy and histological examination for any

acute irritation or inflammation and compared to the contralateral mucosal surface as control. No differential macroscopic or microscopic findings indicative of local irritation of test article effects were observed.

Pharmacokinetic data show that systemic exposure to tropicamide, both in terms of C_{max} and AUC, after oral or intra-oral administration is lower than after ocular administration, suggesting that the NH004 intra-oral thin film formulation safety profile will not differ from the well-documented safety of the standard ophthalmic formulation. The local irritation studies also suggest that the intra-oral formulation should be devoid of major irritating effects.

It is also worth noting that the eye retains about one-fifth of an eye drop, with the remainder entering the circulatory system through conjuctival capillaries and via tears which enter the nasolacrimal duct. Therefore, topical eye drop delivery route can actually have a greater pharmacological effect than oral delivery.

NH004 Clinical Experience

A pilot proof-of-concept study in PD patients who manifested sialorrhea demonstrated that NH004 was safe and exerted anti-sialorrhea effects worthy of further exploration [101]. The study investigated the safety and anti-sialorrhea efficacy of single doses of intra-oral slow dissolving thin films containing tropicamide (NH004) or placebo (Study NH004-2; Clinicaltrials.gov NCT00761137). Nineteen non-demented, idiopathic PD patients who complained of sialorrhea received three doses (0.3, 1, 3 mg) of tropicamide and placebo in random order, separated by 7 days. A visual analog scale (VAS) was used to measure the patient's subjective feelings of saliva levels at baseline and at 15, 30, 45, 90 and 120 min after treatment administration. For the last 7 patients, saliva volume was measured at baseline and 75 min after treatment. Fluctuating patients were evaluated in the ON-condition. The mean age of included patients was 67±12 years, 78% were male, and the median disease duration was 8 years.

A dose and time effect trend of the NH004 intra-oral dissolving films to reduce sialorrhea in PD patients over at least 2 hours was observed and a statistical difference in VAS scores at 120 min favored tropicamide 1 mg films (95% Confidence Interval: -2.57 to -0.48). The effect of the tropicamide containing thin film over time is shown in Fig. (**2**). The mean decrease in VAS score from baseline to 120 min were -0.55±0.54, -1.08±0.54, -1.53±0.52 and -0.81±0.51 for placebo and 0.3, 1 and 3 mg tropicamide, respectively (F=0.6 p=0.6, ANOVA). Saliva volume was reduced by 27%, 33% or 20% after tropicamide 0.3, 1 or 3 mg vs. 5% with placebo (p=0.5, Friedman).

Safety in the NH004-2 study was assessed by laboratory testing, ECG, Mini-mental examination state (MMSE), and clinical evaluation. Clinical laboratory testing was performed at baseline and at the end of the study period. Twelve-lead ECGs were also conducted at baseline and 120 minutes after drug treatment at each visit. Blood pressure and heart rate were measured at each visit, before and 120 min after treatment. Finally, the MMSE was performed at baseline and at the end of the fourth visit. Patients were monitored hourly after the drug (or placebo) administration for the appearance of adverse events with a focus on those known to be associated with systemic administration of anticholinergics such as confusion, pupil dilation, nervousness, fever, irritability and ataxia. No adverse events were observed during the trial.

ECG parameters are shown in Table **6**. No clinically significant differences were noted in any of them. There was a

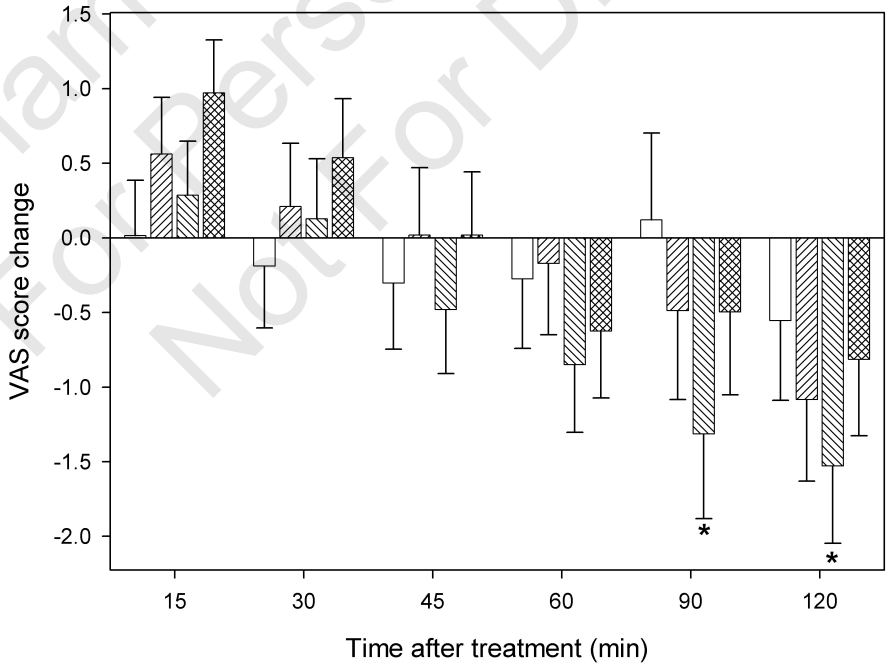


Fig. (2). Effect of Tropicamide containing thin films over time on reducing sialorrhea. VAS = Visual analog scale. VAS score change after placebo (▭) or 0.3 (▨), 1 (▧) and 3 mg (▩) Tropicamide. Means ± standard error of the means are shown. * 95% Confidence interval excludes 0, thus indicating a possible treatment effect with tropicamide 1 mg at particular time points.

Table 6. ECG parameter: Heart Rate (bpm).

	Baseline	Placebo	Tropicamide 0.3 mg	Tropicamide 1 mg	Tropicamide 3 mg
Mean	75.17	71.44	73.19	72.37	69.79
Standard Deviation	21.52	16.77	23.13	22.30	14.83
Standard Error of Mean	5.07	3.95	5.78	5.12	3.40
Median	70.50	70.50	68.00	68.00	67.00
25^{th} percentile	64.00	61.00	60.00	62.00	62.00
75^{th} percentile	80.00	77.00	81.50	77.00	74.00
Maximum	143.00	129.00	147.00	155.00	118.00
Minimum	42.00	50.00	42.00	44.00	45.00

Treatment effect by mixed-effects ANOVA model: F=0.7 p=0.6.

trend for the QTc to be affected by tropicamide, but this was in the direction of greater safety. Other ECG safety measures that were within normal values included PR interval, QRS complex amplitude, QT interval, Corrected T (QTc) and QRS complex axis. There were no differences in the frequency of lab values outside the reference range between baseline and visit 4, as assessed by blood cells, renal, metabolic and liver function values. Mean ± standard error of the mean MMSE scores were 28.9±0.3 at baseline and 29.0±0.4 at the end of the study (p=0.5). These preliminary data suggest that tropicamide 0.3 to 3 mg is probably safe and well tolerated.

Based on the findings of this single-administration dose-finding study, another randomized double-blind, placebo controlled crossover study (clinicaltrials.gov identifier NCT01844648) is underway. This study is designed to demonstrate that NH004 tropicamide (1 mg) intra-oral slow dissolving muco-adhesive thin strips provides better short term relief than placebo thin film strips from sialorrhea symptoms in Parkinson's disease patients when the films are used twice a day, in a home setting, over a period of one week.

Other Uses for NH004

There are also a variety of situations in which it is desirable to temporarily inhibit or reduce saliva production in otherwise healthy individuals. For example, it is often useful or necessary to maintain an adequately dry oral field to perform various dental, orthodontic, periodontal, and oral surgical procedures. It is very important to maintain a dry oral field during many dental procedures, including cementation and bonding procedures, amalgam and composite restorations, the applications of sealants, and impressions during restoration of both anterior and posterior teeth. The increasing reliance of modern dentistry on adhesive materials has renewed the interest in means to maintain a dry field. Undesired saliva accumulation and drooling during such procedures has largely been addressed by employing one or more objects or mechanical devices that must be inserted into the mouth of a patient, e.g., suction devices, cotton rolls, and rubber dams. Such objects and devices can be cumbersome for both patient and the attending oral healthcare professional, interfere with the use of other tools employed in a procedure, invoke a gag response in the patient, and generally contribute to patient distress. Use of NH004 to produce an adequately dry oral field in a patient's mouth that may eliminate the necessity for using various mechanical objects would be highly desirable and would likely enhance patient acceptance of various dental, orthodontic, periodontal, and oral surgical procedures.

SUMMARY

Sialorrhea is a frequent problem in PD and persons with neurologic disabilities. Serious medical and psychosocial problems may result. Current treatment is based on a combination of treatment modalities including drug therapy.

Tropicamide is a synthetic tertiary amine acetylcholine muscarinic receptor antagonist, widely used in eye drops to produce mydriasis and cycloplegia for ophthalmic purposes. Various studies, globally including more than 10,000 subjects, have shown a virtual absence of adverse events when single doses of tropicamide were administered. Additionally, tropicamide has been chronically administered to children in an attempt to control myopia. Even with chronic exposure for years in that population, tropicamide appeared to be devoid of adverse events. Therefore, the benefit/risk ratio for the ocular formulation of tropicamide when used for producing mydriasis and blocking accommodation is positive.

NH004 consists of tropicamide incorporated into a slow dissolving muco-adhesion thin film, which allows release of the drug into the oral cavity. The slow release of the active ingredient maximizes the local effects of the drug and minimizes systemic absorption. The advantages of this delivery means include improved local bioavailability, quick-onset of action, slow dissolution, good organoleptic properties, convenient to administer, and improved patient compliance.

A study in rabbits showed that tropicamide exposure after intra-oral or oral administration was lower than after ocular administration. These findings suggest that tolerability to tropicamide when administered by these routes should be no

worse than when administered by the ocular route. It was also found the tropicamide intra-oral film was devoid of any local irritating effects in rabbits.

A proof-of-concept pilot study was conducted to explore the safety and anti-sialorrhea efficacy of single doses of intra-oral slow dissolving thin films containing tropicamide (NH004) or placebo in Parkinson's disease patients. Tropicamide 1 mg resulted in a significant decrease in the VAS score, as noted in a secondary analysis. No adverse events were detected in any of the treatment sequences. Results of this study showed that NH004 was safe and exerted antisialorrhea effects worthy of further exploration. A double-blind, multisite, clinical study is currently underway.

Overall, current drugs in development for PD show a shift towards long term disease management and NH004 may be part of the supportive care options for PD patients. NH004 is a promising new therapy that may help provide consistent control of salivation to improve hygiene and self-esteem.

LIST OF ABBREVIATIONS

ANOVA = Analysis of Variance

AUC = Area under the Curve

Cmax = Maximal plasma concentration after drug administration

ECG = Electrocardiogram

LD50 = Lethal Dose 50%

mAChR = muscarinic acetylcholine receptor

SD = Standard Deviation

Tmax = Time at Cmax

CONFLICT OF INTEREST

Neal M. Farber and Elkan R. Gamzu hold shares in NeuroHealing Pharmaceuticals. Santiago Perez-Lloret is a consultant to NeuroHealing and has received reimbursement for travel expenses. No writing assistance was utilized in the production of this manuscript.

ACKNOWLEDGEMENTS

This work is partially supported by funding from the Michael J Fox Foundation for Parkinson's Research and from NeuroHealing Pharmaceuticals, Inc.

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Received: June 03, 2014 **Revised: September 08, 2014** **Accepted: October 11, 2014**