

INTERFERENCE OF THE EARLY AND LATE DRUG THERAPY IN PARKINSON DISEASE IN THE MANAGEMENT OF DYSPHAGIA

Interferência do tratamento medicamentoso imediato e tardio na doença de parkinson no gerenciamento da disfagia

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ABSTRACT

Parkinson's disease shows a higher incidence in the elderly population generating progressive motor impairment, which affects several functions, among which stands out swallowing. The purpose of this study is to correlate the dysphagia in Parkinson's disease with immediate and / or late effect of the drug treatment, which directly or indirectly, will interfere with speech therapy management. We carried out a literature review in electronic databases Lilacs, Scielo, Medline and Pubmed from 2001 to 2011, using the free terms "Parkinson Disease" (Parkinson Disease), "swallowing" (deglutition), "dysphagia" (dysphagia), "pharmaceutical preparations" (pharmaceutical preparations), "levodopa", "videofluoroscopy" (videofluoroscopy), a government document (OPAS, 2002), relevant articles and copies of American and Brazilian literature about the theme. The literature appointments levodopa as the main pharmacological treatment of the Parkinson's disease. However, the resolution of the motor symptoms must be balanced in function of important collateral effects, being immediate or later. Actually, there aren't consistent answers in favour of the resolution of the dysphagia in consequence of pharmacological treatment, wich effects may interfere, direct or indirectly, on the dysphagic manifestations and of several ways. In this way, turns fundamental the record of the medications like part of the anamnesis, considering that, such data may help orientation/reorientation of the phonoaudiologic management, specially interdisciplinary context. In despite of possibility of Parkinson's patient to answer inconsistently to pharmacological therapy, is noteworthy that professional must pay attention to presence of collateral effects like modifiers factors of the dysphagia oropharyngea profile in the idiopathic Parkinson's disease.

KEYWORDS: Parkinson's Disease; Deglutition; Dysphagia; Levodopa

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INTRODUCTION

The Parkinson disease is the second neurodegenerative infirmity more common after Alzheimer disease, affects mainly of the third age population^{1,2}, with incidence, principally in the population up to 65 years old, and prevalence of 1 to 2% in the world and 3% in the Brazil³.

Of unknow etiology, is characterized by presence of multiple monoaminergic dysfunction, including the deficit of dopaminergic², cholinergic, serotonergic and noradrenergic systems, that may to explain the symptoms called non-motors (disturbs of sleep, cognitive and depression dysfunctions), which can be associated with several brain regions injured⁴.

Usually of easy diagnostic if of idiopathic-type, but with atypic components, the variety of differential diagnostics is great. Presents slow progression and clinical manifestations predominantly asymetrics³.

The cardinal signals are: rest tremor, bradykinesia, plastic muscular rigidity (presenting or not dentate wheel signal) and postural instability^{4,5}. Other important clinical data include deambulation disturbs, masked facies, alterations of the voice, dysarthria, drooling, sexual dysfunction, cramps, pains, paresthesia, dysphagia, urinary incontinence, intestinal obstipation, micrograph, disturbs of the sleep, bradyphrenia, depression, dementia, cognitive alterations and sensory disturbs^{4,5}. Logeman et al., 1973, suggest in study that the parkinsonian patients are affected for larynx stiffness, important postural disorders, associated involuntary movements and irregular and weak breathing⁴.

Considering to stiffness and bradykinesia, are regularly found in Parkinson disease alterations in the voice, in the articulation of words and in the oropharyngeal deglutition⁶. There are autors that refer, in initial and intermediary stages, are more evident alterations in the phonation and in the articulation of the speech, and in advanced stages arise reports about complaint in the deglutition. Other say that injuries of the deglutition can to appear as initial stages as advanced stages and that the predominant factor refer to apparent symptomatologic board³.

The treatment of Parkinson disease may to involve non-pharmacological measures, like phonoaudiologic therapy, actions that help the patients to compensate the limitations imposed by disease, besides fundamentals, inclusive, to delay the evolution itself. The pharmacological approach involve a group of drugs that possess symptomatic action and, in despite of improve significantly the life quality of the patients, involve a myriad of adverse effects^{5,7}. The surgery treatment will not be discussed here.

Being the deglutition a complex motor activity indispensable to health and survive of the individuals, which commitment is present in the Parkinson disease, this study, in particular, compelling us to better knowledge about the theme. By the way elucidation of informations about Parkinson disease and its manifestations, powerfully succeded from drug treatment, we seek to understand positive and negative effects of the antiparkinsonian drugs about the dysphagic board, besides about general health state of the patient, in a manner to make up bases that support appropriately the phonoaudiologic work.

The purpose of this study self justify by necessity of help the phonoaudiologist to distinguish the

classic and/or secondary manifestations to the use of dopaminomimetic drugs, a relevant subject to the clinical thinking in the phonoaudiologic evaluation and management, considering the risks of bronchoaspiration, dehydration and/or proteic-caloric desnutrition in the Parkinson disease. Such necessity constitutes one of the first steps for differentiated and more effective therapeutic approach.

Thereafter, the intention of the present study is to relate the dysphagia in the Parkinson disease to the early and/or late effects of drug therapy, that, direct or indirect manner, will interfere in the phonoaudiologic management.

■ METHOD

Retrospective study, with bibliographic revision begunned at June 2011 and conducted by search in the eletronic data bases Lilacs, Scielo, Medline and PubMed in the period between 2001 and 2011. Were used the free terms "Parkinson disease", "deglutition", "dysphagia", "pharmaceutical preparations", "levodopa", and "videofluoroscopy". The works were analyzed since adoption of methodology of systematic review. Were found 140 articles, of which, 29 were chosen for to be related with deglutition function, Parkinson disease and drug treatment in the Parkinson disease. Were considered the articles published in portuguese, spanish and english, in according to the limits "humans", "adults above than 19 years old" and "male and female genre". Since the previous knowledge that such works proportionated help to basic explaining of the theme, were added to searched literature a governmental document (OPAS, 2002), articles (Korchonouv, 2010; Bedin and Ferraz, 2003), thesis (Carrara-de-Angelis E, 2000; Gasparim AZ, 2007) and issues of the american literature (Kandel, Schwartz and Jessell, 2000; Schapira and Olanov, 2005; Purves, 2004) that discuss about dopaminergic system and dopaminomimetics drugs, totalizing 42 publications in this study.

■ REVIEW OF LITERATURE

The neurochemistry organziation and the neuromuscular integration are in the base of the motor control, including several parallel pathways among cortical and subcortical areas, specially the basal ganglia. The functional diversity of the motor control is underlying to the complex organization of the mesolimbic, mesocortical and, principally, mesostriatal dopaminergic systems, whose functional network results from a extent integration between dopaminergic, glutamatergic and gabaergic neurons, such as from repertoire of the receptors

correlates⁸⁻¹⁰. Two classic pathways known help in comprehension of the functioning of the basal ganglia. In the named direct pathway, the upper motor neurons are free from continuous tonic inhibition exercised by inner globus pallidus and by substantia nigra pars reticulata on the thalamus; in the indirect pathway, this index of tonic inhibition increases consequently to the activity of subthalamus, thereby, injuring the action of the thalamocortical neurons on the upper motor neurons⁸⁻¹⁰. The substantia nigra pars compacta and the ventral tegmental area send dopamine to striate. The synapses among this substantia nigra pars compacta and the ventral tegmental area self contact in the base of the spine dendritic of the striate cells, near to the synapses between striatal cells and cortical projections, and, consequently, capable to modulate its glutamatergic effects⁸. Thereby, is easy to conclude that, with destruction of the cells of the substantia nigra pars compacta, the inhibitory discharge stays abnormally high, in consequence of the spontaneous activity of the globus pallidus, and the thalamic activation is less probable to occur. In despite of intricate dopaminergic circuitry involved in the basal ganglia, the signaling initialized by different receptors correlates, underlying to the direct and indirect pathways, reflect the modulatory complexity of the basal ganglia on the upper motor neurons.

Among dopaminergic receptors localized in the striatal cells, there are 5 identified human subtypes: type D1 dopaminergic receptors (D1 e D5) and type D2 dopaminergic receptors (D2, D3 e D4). This receptors are defined by capacity to stimulate (type D1) or to inhibit (type D2) the adenylcyclase. This capacity reflects its different interactions with the G-protein, which can to possess the sequences of different amino acids, that justifies the specificity of each receptor¹¹. A nigral axon can to influence both types of receptors in the group of striatal neurons responsible for muscular contraction agonist-antagonist, proportionating the dopaminergic effect on the agonist (acceleration of the contraction) and antagonist (reduction of the tonus) skeletal muscle during the movement¹².

The parkinsonism is characterized by coexistence of brady- or hypokinesia with reduction of the acceleration of the agonist muscle contraction and increase of the tonus and rigidity. Type D1 receptors mediate the inhibition of the muscular tonus and the type D2 receptors promote or accelerate the contraction of synchronized manner during motion under action agonist-antagonist. In the Parkinson disease, with the nanomolar index of dopamine (type D1) low at striatal synaptic cleft, the tonus can not be sufficiently inhibited, inducing to hypertonicity state and apparent muscular rigidity. In

addition, with the begin of the movement, the micromolar index of dopamine necessary for activation of the normal motor act are not reached in the D2 system, culminating in reduction of the capacity of to produce movement (bradykinesia). Without dopaminergic repair therapy, the progressive loss of the production and release of dopamine induces, each time more, a injured stimulation of the type D1 and D2 receptors and worst of the rigidity and bradykinesia in the disease progression¹².

In addition to modulation of the motor actions, injuries of the basal ganglia, also are associated to neuropsychiatry, cognitive and behavioural disorders, reflecting its role in several functions of the frontal lobe, not only associated to the movement⁹. Parallel connections originated from upper regions of the cortex engage prefrontal and limbic regions, for example. Suggests that this modulation is seemed to classic motor pathway, in allusion to the function of to modulate origin and end of functions, such as, planning, working memory and attention, emotional regulation of the behavior and motivation. This may to explain the occurrence of cognitive deficits in the Parkinson disease.

The dopamine, noradrenaline and adrenaline belong to catecholamine (biogenic amines) group, substances classified like little neurotransmitters. The synthesis occurs inside of the presynaptic terminals from the tyrosine amino acid, which is converted, by tyrosine hydroxylase enzyme, to dihydroxyphenylalanine (levodopa), in a reaction that depends of oxygen like cosubstrate and the tetrahydrobiopterin like cofactor. The levodopa is, so, decarboxylated by aromatic amino acid, the DOPA decarboxylase, and yet are produced dopamine and carbonic gas. As supracited, after released, the dopamine links to specific dopaminergic receptors and the some β -adrenergic receptors. The dopamine is removed of the synaptic cleft by recaptation to inside of nervous terminals or inside of next glial cells by one Na-dependent transporter (the main involved in catabolism are monoamine oxidase and catechol o-methyltransferase). Though dopamine do not cross easily the blood-brain barrier, it is possible to levodopa. The levodopa is absorbed in the small intestine, but is rapidly catabolized in the gastrointestinal tract and peripheral tissues.

The process of degeneration of nigrostriatal dopaminergic neurons induces reduction of the striatal dopamine modulation and, consequently, motor alterations. This model preconize that, increasing the dopaminergic stimulation or reducing the cholinergic or glutamatergic stimulation, the symptom resolve. The drug treatment would must, at least, to include the neuroprotection (reduction of the progression of the disease) and the symptomatic

treatment (control of the symptoms). The neuroprotection is a objective yet not achieved, because the randomized and controlled clinical symptoms are insufficient to show that such drug has this property. Thereby, the symptomatic treatment is the choose for parkinsonian patients and with resultant incapacities⁷.

The selection of the accepted drug must to consider the stage of the disease, the

symptomatology up to date, occurrence of side effects, age of patient, besides of the medications in practice and the cost of the ones. Thereby, there are, actually, several ways of symptomatic pharmacologic intervention. The figure 1 shows a resume of all described medications in the guideline of the OPAS (2002), associating benefits, pharmacokinetic and recommended diary dose:

Drug	Desired Benefit	Pharmacokinetic and Posology	Indicated Diary Dose
Levodopa (release pattern)	Alleviate of the motor symptoms. Efficacy defined in 30 years of use.	Achieves maximum seric index in 15 to 45 min. Needs association to dopadecarboxylase inhibitors (carbidopa or benserazide). Half-life: 60 to 120min.	Available commercially: L-Dopa/carbidopa(ID): 100/10mg, 100/ 25mg/ and 250/25mg; L-Dopa/benserazide (ID): 50/12,5mg, 100/25mg and 200/50mg; Ajdustments as clinical performance.
Levodopa (controlled release)	Like pattern L-DOPA, however, there are not evidences of efficacy in the prevention and control of motor complications. The use before to sleep, in one dose, is importante to alleviate nocturnal and diurnal incapacity and during awake..	Absorbed in the GIT of control mode. Maximum concentration: 45 to 90 min. Needs dose higher than pattern L-DOPA by presenting low bioavailability.	Available commercially: L-Dopa/carbidopa: 100/25mg and 200/50mg; L-Dopa/benserazide: 100/25mg; Adjustments as clinical performance
Pergolide (AD) (D1 and D2 receptors predominant in D2 receptor)	Symptomatic improvement in initial phase at monotherapy, in patients without previous treatment; at advanced phase, when associated to L-DOPA, are efficacies in the control of the motor complications and dyskinesias.	Achieves plasmatic index in 60 to 120 min. Half-life: 24h.	1,5 - 3,5 mg/day dealed in 3 times to day
Bromocriptine (AD) (higher affinity to receptor D2 and partial affinity to D1 receptor). Also shows affinity to noradrenergic and serotoninerbic receptors.		Achieves seric index at 70 to 100 min; bioavailability: 10% (90% suffer first passage metabolism in thte liver). Half-life: 6 to 8 hours.	7,5 to 70 mg/day, necessiting be increased as clinic response and tolerability.
Pramipexole (AD) (preferential affinity to D3 receptors, acting in D2 and with low affinity to non-dopaminergic receptors).		Achieves maximum seric index at 60 to 180 min. Bioavailability: 10% (90% suffer first passage metabolism in the liver). Nearest half-life: 10h.	2-4,5mg/day 3 times/day with criteriously gradual increase.
Cabergoline (AD) (selective to D2 receptors, with affinity to noradrenergic and serotoninerbic receptors)		Achieves maximum seric index at 2,5 hours. Metabolized in several metabolites. Half-life: 65 hours (enables diary dose regimen)	2-5mg/day
Selegiline (MAO inhibitors)		Efficacy in the symptomatic control of the disease at monotherapy: associated to levodopa, there are not sufficient evidence the prevents or control motor complications of the Parkinson disease.	Absorbed by GIT and rapidly metabolized in liver. Its principal metabolites have weak central activity and achieves maximum seric index at 30 to 120 min after oral dose.

Drug	Desired Benefit	Pharmacokinetic and Posology	Indicated Diary Dose
Tolcapone and Entacapone (COMT inhibitors)	Administered simultaneously to L-DOPA, are efficacies in the management of the control of the motor fluctuations. Increase the "on" period and decrease "off" period. Benefits to the long term were not defined.	Tolcapone: achieves maximum seric index at 1,4 to 1,8 hours. About of 20% of the drug is metabolized initially and the remaining links to the plasmatic proteins. It is completely metabolized before of its excretion. Entacapone: achieves maximum seric index at 0,4 to 0,9 hours. 98% flows linked to plasmatic proteins. It is metabolized in the liver and excreted by way of feces (80 a 90%) and urine.	100mg, 3 times/dia 200mg, 4 to 10 times/day
Biperidene e Trihexyphenidyl (Anticholinergics)	Reduction of the tremor, bradykinesia, rigidity and drooling, as well as, improve of the gait and of the speech. Recomendated in younger patients, when rest tremor is dominant symptom.	Absorbed by GIT and, because be lipophilic, cross the blood-brain barrier easily. The Trihexyphenidyl achieves maximum seric concentration at 120 to 180 min and have duration of 1 to 12 hours.	Trihexyphenidyl: 0,5 to 1mg/day Biperidene: 2 to 8 mg/day OBS: the treatment with anticholinergic do not must be abruptly interrupted because of the risk of rebound effect and worse of the parkinsonism
Amantadine (Antiglutamatergic)	Helps in the control of the dyskinesias, as in monotherapy as associated to anticholinergic or L-DOPA.	Absorbed by GIT, achieves maximum seric index at 1 to 4 hours, presenting clinical effect of 8 hours. It is poor metabolized (90% of the ingested drug is eliminated by renal route).	200-300mg/day, 2 to 3 times/day

Source: Clinical Protocol and Therapeutic Guide, created by Health Panamerican Organization, at 2002.

Legenda: GIT, Gastrintestinal Tract; PD, Parkinson Disease; MAO, Monoamine Oxydase; COMT, Chatecol-O-Methyltransferase; D1, D2 e D3, Dopaminergic Receptors; DI, Dopadecarboxylase Inhibitor; DA, Dopaminergic Agonist.

Figure 1 – Medications utilized in the treatment of the Parkinson disease.

The principal substances utilized in the treatment of the PD:

Among available drug therapies for Parkinson disease, the levodopa therapy, also called L-DOPA, have demonstrated better efficacy^{13,14} and low mortality, receiving large indication in the Parkinson disease treatment¹⁴.

In despite of the therapeutic benefits achived with the use of the L-DOPA, its peripheral metabolism (outside of central nervous system) by decarboxylases-type enzymes prejudices the dopamine biodisponibility (product from the L-DOPA metabolism) and produces side effects, specially gastrointestinal ones. Thereby, the administration of L-DOPA associated with decarboxylase inhibitors (considering that such inhibitors don't cross the blood-brain barrier) improve the dopamine biodisponibility in the central nervous system, demanding lower doses, besides of to reduce undesirable effects¹³⁻¹⁵. Noteworthy that the use of the L-DOPA associated with such inhibitors provides more stable and longer effects, and, consequently, the treatment

can to extend to months or years¹⁴, retarding the appearing of motor complications that regularly follow itself to the prolonged use of the L-DOPA. Regularly, individuals with Parkinson disease under prolonged use of the L-DOPA present motor fluctuations and dyskinesias^{16,17}, presenting the known phenomenon like *wearing off* (shorter duration of medication effect), *sudden/random on-off* (gravely sudden of the symptoms of the Parkinson disease) and *delayed ons or dose failures* (initial later of the drug action)^{13,17}. Thereby, with the progression of the disease, events of the freezing, postural instability, besides autonomic dysfunctions and dementia are presented and such patients don't answering more to the treatment of the desirable manner⁷.

Like preventive action to the appearing of the motor complications secondary to the prolonged use of the L-DOPA, specially in stages more advanced of the disease, the method of choice have been the simultaneous use of this one with dopaminergic agonists^{5,7}, of which can be exemplified

anticholinergic, antiglutamatergics and monoamine oxidase (MAO) inhibitors⁷.

Dyskinesias, motor fluctuations and psychiatric symptoms are common complications in Parkinson patients in more advanced stages and with prolonged use of the L-DOPA¹⁷. The clozapine, neuroleptic and antipsychotic drug and with inhibitory action on the dopaminergic receptors showed positive effects in the control of the symptoms ones, without, however, to interfere in the motor deficiency board^{16,18}. The amantadine, like classically described, exerts pre- and postsynaptic dopaminergic action, mild antiparkinsonian activity and come being used like antidyskinetic agent¹⁹.

Noteworthy that, in despite of the advantages of the symptomatic treatment, all this substances bring themselves undesirable side effects. Such effects can be motors or non-motors¹⁷ and some of this ones achieved the point of to limit the use of the substance. The clozapine, for example, may to cause a myriad of effects that limit the use, like excessive sedation, drooling, dry mouth, vomit, weakness or muscle spasm, dyspnea, tremor, neutropenia, thrombocytopenia, urinary incontinuity, epigastric pain and diarrhoea, sickness and grave intestinal constipation, diplopia, hallucination and agitation^{16,18}. Among cholinergic adverse effects, include deficits of memory, hallucinations, sedation and ailment. Secondary dyskinesias, when occur, are focal, resulting in blepharospasm, oromandibular dystonia, torticollis and essential tremor. Other muscarinic effects include dry mouth, constipation, sickness, blear sight, urinary retention, disorders of transpiration and tachycardia. In according to antiglutamatergics, its side effects generally are mild and include insomnia, anxiety, dizziness, disorders of motor coordination, nervousness, sickness and vomit. Vocal myoclonus and peripheric neuropathy occur scarcely²⁰.

Motor aspects of the deglutition in the PD:

Several authors afirm that the incidence of dysphagia is variable in the Parkinson disease, characterized by no symptoms²¹ and rarely refered by patients, that limits the early knowledge for approach. Monte et col., 2005, expose that dysphagia in the Parkinson disease presents of silence manner or refered with asphyxia, multiple deglutitions and regurgitation, being related in up to 70% of the cases²².

Lim (2008), afirm that the literature not have agree about the relation between the severity of the Parkinson disease and presence/severity of the dysphagia. Some studies did not find any relation among this factors, while others studies found worsen of the dysphagia during increase of

the severity of the disease^{23,24}. Suggests that the patients can to experiment symptoms of dysphagia later at the course of the disease in comparison with the others parkinsonian disorders. In despite of this, because of the poor correlation between the related symptoms and the instrumental evaluations, presymptomatic dysphagia can be present and not identified²³. Azevedo and Cardoso (2009) refer that the parkinsonian individuals present complaints related to disorders in the deglutition at advanced stages and hypothesized that this occurs because reduction of the sensibility in the aero-digestory tract⁵.

The respiratory insufficient because dysphagia and aspiration is considered ththe principal cause of death of the disease^{3,5,22,23,25}, that can be related with the presence of the dysphagia, associated to the difficult that the patients possesses in to locomote²³. They can be more susceptible to swallowing at insufficient times of the respiratory cycle, that is, during the inspiration or during the production of poor subglotic flux. Also, there is tendency to inspiring after deglutition, independent of to swallowing at inspiratory stage. If the larynx is considered like a organ with regulatory capacities associated to function of deglutition, the stimulation of subglotic mechanoreceptors by expiratory aereo flux before of the deglutition sends signals to a "pattern generator", localized in the brainstem. This answer in velocity and muscle strength of proportional manner to the subglotic pression exerted. Such thinking may explain partially why the antiparkinsonian drugs do not improve consistently the deglutition function or do not prevent the progression of the dysphagia²⁶.

Considering the capacity of the protection of the air pathway, studies discuss that, in some patients, the hability in to produce effective voluntary cough is compromised because of the rigidity of the thoracic wall, culminating in reduction of the pulmonary capacity and perturbing the production of the subglotic air pressure necessary to deflagration of the cough²⁷. Miller (2011) verified in your assay that some patients with Parkinson disease did not present cough during and after repeated deglutitions, speculating that the same patients did get reducing the index of ingest through shorter and frequent deglutitions, or simply stopping the ingest, waiting to avoid penetration and/or aspiration²¹. Vey times, like occur wih the dysphagia, the individuals are unconscious of the injured pulmonary function, thereby, such problems are not perceived until that appear more several disorders²⁶.

Dentary problems may occur because the lack of orofacial muscle control, reduced saliva and compromised manual control, having also relating to cognitive deficit²⁹. Bloem et cols. (2009) related

the case of a patient of 71 years old with increased salivation and drooling, conducting to perioral lesions²⁹. Lamonica (2003) shows, in research about clinical manifestations in the Parkinson disease, dysphagia related by 50% of the patients and drooling in 70% of the interviewed patients³⁰. The dependence to eat and take a oral care, eating by tube, several medical diagnostics, smoking and quality of teeth are important predictors²⁵.

At 1983 Logeman proposes the swallowing videofluoroscopy, with possibility of to evaluate the dynamic of the full process of the oropharyngeal deglutition, being analyzed disorders of oral phase, like tremor of phonoarticulatory organs, difficulties in the initial production of the alimentary bolus, reduction of the salivar secretion index, increase of the deglutition time, limitation of the projection of the tongue and mandible during chewing and presence of the repeated anteroposterior movements of the tongue for propulsion of the bolus ("festination of the tongue muscle"); in the pharyngeal phase observed start delayed, with stop of the bolus in the vallecula space and in the piriform sinus, with risk of larynx penetration and aspiration, alterations of pharynx motility and of the cricopharynx function; in the esophageal phase occurred peristalsis reduction, with shorter transit time³. All this disorders discussed reflect the desintegration of the automatic and voluntary movements caused by akinesia, bradykinesia and rigidity, characters of the Parkinson disease. In study with sample of 15 parkinsonian patients, 15 cerebral vascular accident-suffered patients and 14 health control patients, followed in videofluoroscopy exam, the parkinsonian patients presented alterations in the dynamic of the deglutition oral phase, probable to culminate in penetration and/or aspiration. As parkinsonian patients ascerebral vascular accident-suffered patients showed reduced ejection power (demanding more time of oropharyngeal transit) or so, the called "ejection in two times", which oral content is swallowed with penetration of little content in the pharynx followed by swallowed rest bolus in continuous act³¹.

During videofluoroscopy evaluation of the deglutition of elder parkinsonian patients, Bigal et cols. (2007) observed seemed manifestations to the found for Logemann (1983), including the difficulties in the formation of the bolus, inadequate labial

closing, multiple deglutitions, terciary contractions of the esophageous and gastroesophageal reflux³². When qualitatively analyzed, was observed compatibility of the complaint of sensation of food stopped in the throat, remaining in valleculae and piriform recess, as well as necessity of successive deglutitions. The results of the Sung et al. (2010) suggests that the existence of pharyngeal and esophageal dysfunction, same before clinical manifestations of the dysphagia, may to reflect involvement as of the brainstem as of the myoenteric plexus at early stages of the disease²³. Gasparim (2007) analyzed the efficacy of the deglutition and the cough reflex in cases of laryngeal penetration and/or tracheal aspiration by food, in different stages of severity of the Parkinson disease and observed that deglutition was efficacious for the foods with liquid and solid consistency in parkinsonian patients at 1 to 2,5 stages of the staging scale of Hoehn & Yahr (1976); and the pasty consistency in parkinsonian patients at stages 1 to 4; the cough reflex was efficacious for the pasty food at stages 1 to 4³⁴.

There are still other reports about alterations in the oral, pharyngeal and esophageal phases of the deglutition^{24,25,31,35}, such as: 1) the prejudice of the ejection power, producing increase of the oropharyngeal transit time or swallowing of the oral content in two steps (in the first step, the swallowing of little alimentary bolus in the pharynx is followed by rest mass in continuous act)³¹; 2) more time in the oral transit attributed to the tongue festination phenomenon, described by Troche (2008), suggesting that such phenomenon may be associated to the bradykinesia, rigidity and voluntary behaviour of the oral phase of the deglutition²⁵; 3) abnormal increase of the rest pressure of the pharynxesophageous transition, which, in despite of do not be the main factor of the dysphagia, may be present in some patients preceding the others alterations of deglutition and, maybe, to result in stop of the bolus at piriform sinus, culminating in larynxtracheal aspiration³⁵.

Bramble et al, cited by Fuh et col. (1997), that focalize in to study the esophageous, suggests that cholinergic mechanisms and not only dopaminergic ones, are important to deglutition control³⁶. Scarce studies have demonstrated, objectively, the drug treatment effects in the functions of deglutition and speech, as is showed in figure 2^{3,19,22,23,36-40}.

Dysphagia and medicamentous treatment in the PD.

In despite of rare evidences about the effects of the levodopa during swallowing²³, affirms that oropharyngeal dysphagia in the idiopathic Parkinson disease is inconsistently responsive to pharmacologic therapy²⁶. Some researchers already examined the deglutition process in a group of patients in different periods (in whatever moment, under dopaminergic effect; in other moment, without use of dopaminergic drugs) and discovered that the abnormalities, generally persist after administration of drugs, in despite of the increase of dose²⁶, or demonstrate only low improve in dysphagia in a group of participants, with decline of the function in other²³. Other research only shows low improve in the dysphagia in a group of participants and worsen of the dysphagic board in other one²³. There are studies that relate reduction of the full time of the deglutition and improve of the buccal lingual facial motricity in patients treated with apomorfine,

however, other studies shows that dysphagia is predominantly refratary to dopaminergic drug action and there are cases that worsenes with levodopa administration. Absent of clear association between motor dysfunction and abnormality of the deglutition, added to lack of benefit of the levodopa in some cases, brings to think about the involvement of other neurotransmission system with the deglutition disorders found in the Parkinson disease.

By the other hand, other side effects can interfer of direct or indirect manner in the swallowing. Excessive sedation, diurnal sleepness, depression and psychotic disturbs, whether not limit the patients of to go the sessions, are sufficient to difficult ever therapeutic planning. The lack of adequate alert may to conduct the individual to do not feed adequately, compromising the nutritional board and, also, to get capsules by oral administration. Sickness and vomit maybe limit the access to phonoarticulatory organs during evaluation or therapy. Dizziness, postural hypotension and balance disorders certainly will

Author	Draw of the Study	Drug	Dose mg/day	Interval for Evaluation	Clinical Evaluation / Exam	Results
Hunter et col., 1997 ³⁷	15 parkinsonian patients (12 FG and 3 MG)	Levodopa + Apomorphine	Not Refer	Was removed Levodopa/ Apomorphine 8h before and after fasting of 4h.	In the first day was realized motor evaluation (to walk/ to sit) + evaluation of deglutition with barium ("off" motor). Already after, administrates a dose of Levodopa 250mg/Carbidope 25mg and re-evaluatethe deglutition ("on" motor). In the second day, the procedure is repeated, but uses dose of 3,5mg of Apomorphine.	<ul style="list-style-type: none"> - improves of the motor response as with the use of L-DOPA as of Apomorphine; - In respect to deglutition, do not observed significative difference; - after the use of Apomorphine observed decrease of accumulate in valleculae and of pharyngeal transit time for semiliquid consistency; - with the use of levodopa was seen decrease of the number of deglutitions for clearance, decrease of the time of preparatory oral phase for semiliquid and liquid consistencies and increase of the time of oral phase and total time of the deglutition for solids.
Fuh e col., 1997 ³⁶	19 pr with PD	Levodopa	Not Refer	Before and after administration of L-DOPA (60-90 min.)	Videofluoroscopy (VDF) with liquidpasty and solid consistencies	<ul style="list-style-type: none"> - alteration of the deglutition in 12 pr (63,2%), having improvement of the symptoms in 50% of this patients after administration of the Levodopa; - the oral phase was altered in 6 pr: oral transit increased (4 pr), elevation of the lingual base decreased (3 pr), anterior-posterior moviment of the tongue decreased (1) and oral tremor (2), in a such way 3 pr presented better performance after L-DOPA (2 pr presented better performance of the tremor of tongue and 1 pr presented better elevation of the lingual base) and 11 pr presented alteration of pharyngeal phase, in a such way 1 pr worsened after L-DOPA; - the laryngeal aspiration was observed in 3 (15,8%) pr, with 2 pr after Levodopa and 1 pr during and after the deglutition. Of these 3 pr, 2 did not aspirate after L-DOPA; - still, relate that the results of the VDF do not correspond to the symptoms. Initial PKS that not presented symptoms, obtained high percentage of abnormalities in the objective evaluation, principally, residuals in valleculae and piriform sinusis and delay in the triggering of the deglutition.

Author	Draw of the Study	Drug	Dose mg/day	Interval for Evaluation	Clinical Evaluation / Exam	Results
Carrara-de Angelis, 2000 ³⁸	24 pr with PD: - 18 MG; - 06 FG; Hoehn & Yahr: 2 a 4	Not Refer	Not Refer	-	- Phonoarticulatory clinical evaluation; - Computerized acoustical evaluation of the voice; - Videolaryngeal estroboscopy; - Videofluoroscopy of the oropharyngeal deglutition;	- PD Pr – more symptoms and more awareness of the alterations of the oral communication than of the alterations of the deglutition; - Alterations of the phonoarticulation more frequent – reduction of the loudness and articulatory imprecision, both correlated to the decrease of the speech intelligibility; - The larynx presented glottic cleft predominantly fusiform, tremor of larynx and of vocal folds and mixed supraglottic constriction. Besides, the acoustic measures of perturbation and of noise showed values over of the normality; - Alterations of the deglutition – evidents in all the phases of the deglutition, with 33% of the patients presenting silent aspiration; - Measures of the perturbation of the fundamental frequency showed significant association, with the larynx penetration;
Monte et col, 2005 ²²	15 DP 12 NDP 07 control	L-Dopa	DP: 977,2± 386,5 NDP: 513,8± 261,0	After 1-2h. administration	Hoehn & Yahr staging and UPDRS II ("on" period) and III; VDF with liquid and lot of bread contrasted with barium.	- pharyngeal retention of liquid and solid and lower efficiency of the deglutition in non-dyskinetic patients when compared with the controls. - dyskinetic patients tend to a better global performance of the deglutition (however, with adjusted dose, the difference tend to disappear) and the lower time of the oral transit because of the higher doses of Levodopa, when compared to the non-dyskinetic patients. - the Levodopa improves the deglutition in only some patients.
Belo et col, 2009 ³	Elder: 15 without neurological disease (EWND); 15 with PD.	Not Refer	Not Refer	After 3h administration	Electromyogram of the right and left supra-hyoid-digastric musculature - 10 ml of water; - 10 ml of fine pasty diet; - deglutition under command (03 times)	- the medium of the amplitude RMS*was lower in the elder with PD than in the ISDN; - was observed that the right side was higher than left side in the two groups; - significative differences among consistencies; - To the separating the individuals with PD in according to sides higher and lower injured by neurologic disease were found lower media in the lower injured side, as in the liquid (water) as in the fine pasty (yogurt) consistencies. This difference was little, when compared to the data separated in right and left sides; - the medium found for the duration of the muscle contraction during deglutition of pasty foods was longer than liquids in both groups of individuals. And the medium duration of the contraction in the elder individuals with PD was mildly longer than in the ISDN. However, this difference do not achieved the significance.
Lim, 2008 ²³	10 PD in the "on" and "off" periods	Levodopa			- UPDRS; - Coordenation breathing x deglutition; - Test of the deglutition time; - Test of pulmonary function; - Qualitative evaluation of the deglutition;	LEVODOPA "ON": - Minor volum per deglutition (NS); - Reduction of the pulmonary function (S); - Reduction of the deglutition efficiency, but without apparent increase of the risk of aspiration; LEVODOPA "OFF": - Increase of the score of the motor exam (S); Obs: did not have difference in the coordination between breathing and deglutition or qualitative evaluation of the deglutition;

Author	Draw of the Study	Drug	Dose mg/day	Interval for Evaluation	Clinical Evaluation / Exam	Results
Gomide et col, 2008 ¹⁹	43 patients: 17 DP; 15 psychotics; 11 DP and psychotics. MA= 64 years old; Medium UPDRS: 55 points. .	Clozapine	Medium of the maximum dose: 70 mg/day	-26 patients used the medication during approximately 3,5 years	- Clinical observation	- improve of the clinical board in 29 patients; 9 remained with stable clinical board. The treatment was stopped in 20 individuals, being 9 for adverse effects. - lower tolerability: 26 individuals (60,5%) presented adverse clinical effect after beginning of the treatment ; of this, 9 refer over of 1 side effect, such as, excessive sedation(13), drooling (7), neutropenia (3), thrombocytopenia (1), urinary incontinency (1), epigastric pain and diarrhea (1), sicknesses, vomits and obstipation (1), diplopia (1), hallucination (1) and agitation; (1); - 22 (51,2%) patients presented partial improve, while 7 (16,3%) had significative improve of the clinical board with the use of Clozapine. 9 (20,9%) did not have improve and the last 5 had the treatment stopped before that the result was correctly evaluated; - improve of the psychotic and motor symptoms was observed in 65,4% and 64,3% of the participants, respectively.
Coriolano et col, 2010 ³⁹	2 without PD, FG 1 healthy individual of 60 years old Age: 63 years old Hoehn Yahr = 3 at "off" period	Not Refer	Not Refer	Not Refer	SURFACE ELECTROMYOGRAM (orbicularis oris, masseter , suprahoid and infrahyoid) -1 st condition – single deglutition of a volum offered for non-reusable plastic syringe. The subject was oriented to maintain the content inside the mouth and to swallow after command: water – 10ml and 20ml; yogurt of hard consistency - 5ml and 10ml. -2 nd condition – free swallow of water: non-reusable plastic glass containing 100ml. After record of 2s of the EMG, the researcher announced he command to swallow.	- the normal subject made a single deglutition of 20ml of water, while the subject with PD needed of two deglutitions for the same condition; in the free deglutition, the normal subject made 6 deglutitions in 10s, while the subject with PD made 4 deglutitions (6 versus 4) in the same condition; - In the subject with PD was necessary a longer time than 10s for free deglutition of the 100ml of water. Still, observed a longer time interval among 4 deglutitions realized by subject with PD in the condition of free deglutition at time of 10s in relation to the normal subject. - The medium of amplitude RMS of the normal subject was higher in all the channels than the medium of amplitude RMS of the two deglutitions of the PD subject; this characteristic was observed in the single deglutition of the volumes of 10ml and 20ml of water. - The duration of the electromyographic activity of the normal subject was lower in all the channels than the duration of the two deglutitions realized by subject with PD in the single deglutition of 10ml and 20ml of water; - In the volumes of 5ml and 10ml of consisten yogurt, in both subjects, have only one deglutition; - The duration of the electromyographic activity in the single deglutition of 5ml and 10ml of consisten yogurt in the normal subject was lower than the duration of the deglutition of the PD subject in the same condition; - Both subjects presented only one deglutition to the volumes 5ml and 10ml of consisten yogurt.

Author	Draw of the Study	Drug	Dose mg/day	Interval for Evaluation	Clinical Evaluation / Exam	Results
Gasparin et col., 2011 ⁴⁰	- 38 PD; - 38 WND. Dealing of the groups as Scale of Staging of HOEHN & YAHR (1976) modified: - subgroup 1 (stages 1 and 1,5): 07 pr (18,4%); - subgroup 2 (stages 2 and 2,5): 19 pr (50%); - subgroup 3 (stage 3): 08 pr (21%); subgroup 4 (stage 4): 04 pr (10,5%).	Not Refer	Not Refer	Stage "on" or 4 hours after ingestion of the drug.	Nasalfibrouslaryngoscopy	- Liquid alimentary consistency: effective deglutition in 13 individuals (34,2%) of the experimental group and in 32 individuals (84,2%) of the control group ; major occurrence of stasis was in the region of the piriform recesses; - Pasty alimentary consistency: deglutition was effective in 7 pr (18,4%) of the experimental group and in 26 individuals (68,4%) of the control group; major incidence of stasis was in the piriform recesses; - Solid alimentary consistency: 17 pr (44,7%) of the experimental group and 29 individuals (76,3%) of the control group do not have stasis; major occurrence of stasis at region of epiglottic valleculae; - Laryngeal penetration: in relation to the liquid consistency, was manifested in 6 pr of the subgroup 2, 3 pr of the subgroup 3 and 3pr of the control group; in relation to the pasty consistency, occurred in 4 pr of the subgroup 2, 2 pr of the subgroup 3 and absent in the control group; in relation to solid consistency, occurred in 1 pr of the subgroup 1 and absent in the control group; - Tracheal aspiration: in relation to liquid consistency, in 5 pr of the subgroup 2 and in 1 pr of the subgroup 3; absent in the control group; - Cough reflex in the occurrence of laryngeal penetration was not efficacy in 5 pr of the subgroup 2 in the liquid consistency and, of this, in 4 in the pasty consistency. In the control group the cough reflex was efficacy in the 3 cases of laryngeal penetration in the liquid consistency; - Silent aspiration was observed in 5 pr in the subgroup 2 and absent in the control group.

Subtitles: PD, dyskinetic patients; PND, non-dyskinetic patients; im, average age; SF, female; SM, male; DP, Parkinson Disease; S, significant; NS, non-significant; pr, patient; ppv, vocal folds; *RMS is the square root of arithmetic average of the square values of the digital electromyogram in a time frame. This average is used in all cases of those that there are variations of negative and positive values. From this calculus negative data become positive.

Figure 2 - Comparison of 9 studies that relate drug actions to the deglutition disorders found in Parkinson Disease

induce the examiner/therapist worries in put the patient at comfortable and appropriate postural, avoiding falls and proportionating him security. Weakness, muscle spasm, increase of tremors, coordination disorders, ataxies, dyskinesias, involving the appendicular or axial musculature, will can to have interference with major or minor punctuality. Mainly for the neurologic patients, the body postural maintenance is indispensable during the meals. In this context, is simple to understand that to assume different specific postures may to injury the swallowing. Motor alterations involving specific muscular groups of the deglutition may interfere directly in its performance. The drooling and sensation of dry mouth generally cause discomfort

to patient, however, in the impossibility of to change of the medication, we can help him to control major volume of the saliva or betake to measures that alleviate the sensation of dry mouth.

Is important to emphasize, also, that a diet rich in protein may to influence the distribution of the levodopa to blood stream and to central nervous system of negative form, because both compete in the gastrointestinal tract and in the blood-brain barrier. At advanced phases of the disease, this will culminate in a major time between drug ingestion and its action. Initially, because of the presence of residual neurons, this latency do not occurs. In such way, the diet of the patient would must be specially adjusted, with administration of levodopa

one hour after of the meals, in times away from protein ingestion (and this , two hours after the levodopa ingestion or to the final of the day), with empty stomach, or, still, simultaneously to the diet rich in carbohydrates, which will facilitate the intestinal absorption⁵. Juri and Chaná (2006) suggests the levodopa administration, at least, thirty minutes before of the meals like a important measure to optimize the kinetic of the drug². Thereby, in the desire to utilize, in a evaluation or therapy, a meal rich in protein, may be necessary to adjust the time of the intended attendance.

The professional must to know the medication that is being administrated to the patient, to familiarize yourself with “on” and “off” periods, besides to pay attention to “wearing off”, “sudden/random ‘on-off” and “delayed ons” phenomena. It is possible that the patients avoid to feed themselves at “off” state. Still, the extending of this interval will may to reduce the total quantity of diary alimentary ingestion, culminating in desnutrition. This fact induces us to think that would have difference in the moment of to care of the patient, that is, at “on” or “off” periods, obtaining, during “on” period, the better global motor rebound.

In general, at first contact with the patient, must be collected data, such as, disease duration, hour desired of the patient to realize your meals, medications in use and its posology and diary activity. Besides of the detailed investigation of the existence of symptoms and/or signals of dysphagia, must be asked whether the patient is under one or more effects of the administrated drugs. Such approach will stimulate the clinician to analyze the collected data with desire to distinguish the origin of the disorders. Besides, will can to define a corrective or attenuater therapeutic approach of the problem.

Besides of choice of the adequated exercises, maneuver and consistencies for each case, is needed to consider the possibility to readjust of the food options with a nutrition professional, with the finality of bypass the incompatibility between protein and levodopa in the gastrointestinal tract, as cited. Other important aspect is that the patient can to feel better performance when is at “on” period of the

medication and such fact to culminate in absences to the therapies when the same be with grave rigidity and difficulties of locomotion at combined hour to attendance. However, must give preference, specially in the first attendances, to the period that medication present itself active.

Considering the prevalent age group in the Parkinson disease, would be interesting to value the prevention of cognitive deficits, inclusive, by exposed in this review, about the relation between the basal ganglia and cortical and limbic areas. For example, since that perceives that the effects of the medication contribute for the limitation of the diary life activities, this must be related to the clinician (mainly because of the major frequency of contact between therapist and patient). Besides, other more specific approaches may be executed, obviously, as a therapy of group focalized to cognitive stimulation.

■ CONCLUSION

The discussions in the literature occur principally in turn of the levodopa, pointing it like a main pharmacologic treatment of the Parkinson disease. Several drugs are utilized in the treatment of this disorder. Until moment there are not consistent answers in favour of resolution of the dysphagia like result of pharmacologic treatment. The drugs alleviate the characteristic motor symptoms, however, at costs, of imediate or later, motor or non-motor side effects. Some of the non-motor effects present direct or indirect interferences about the dysphagic manifestations; motor effects may interfere in ever deglutition phase and to potentiate the existing difficulties; there are, yet, the risk of interferences about cognitive aspects, limiting ingestion by oral pathway, because of the voluntary and aware aspect of the some deglutition phases. Suggests the record of the medication utilized by the patient (and respective posology) and reflection about possibility of interferences of the pharmacologic therapeutic about the dysphagic board and general health state of the patient, intending bypassing it or removing it, since that possible, at interdisciplinary context.

RESUMO

A Doença de Parkinson apresenta grande incidência na população idosa, gerando comprometimento motor progressivo, que afeta várias funções, dentre as quais se destaca a deglutição. Esse trabalho teve como objetivo relacionar a disfagia na Doença de Parkinson aos efeitos imediatos e/ou tardios do tratamento medicamentoso, que de forma direta ou indireta interferirá no gerenciamento fonoaudiológico. Fizemos uma revisão de literatura nas bases de dados eletrônicas Lilacs, Scielo, Medline e Pubmed no período de 2001 a 2011, utilizando os termos livres “Doença de Parkinson” (*Parkinson Disease*), “deglutição” (*deglutition*), “disfagia” (*dysphagia*), “preparações farmacêuticas” (*pharmaceutical preparations*), “levodopa”, “videofluoroscopia” (*videofluoroscopy*), além de um documento governamental (OPAS, 2002), artigos relevantes e exemplares da literatura americana e brasileira sobre o tema. A literatura aponta a Levodopa como o principal tratamento farmacológico da doença de Parkinson. Contudo, a melhora dos sintomas motores deve ser ponderada em função da ocorrência de efeitos colaterais importantes, sejam imediatos ou tardios. Até o momento não há respostas consistentes a favor da melhora da disfagia como resultado do tratamento farmacológico, cujos efeitos podem interferir direta ou indiretamente sobre as manifestações disfágicas e de várias formas. Assim, torna-se fundamental o registro das medicações como parte da anamnese, considerando que tais dados possam auxiliar na orientação/reorientação da conduta fonoaudiológica, especialmente em contexto interdisciplinar. A despeito da possibilidade do doente de Parkinson responder de forma inconsistente à terapia farmacológica, vale ressaltar que o profissional deve estar atento à presença de efeitos colaterais como fatores modificadores do quadro de disfagia orofaríngea na Doença de Parkinson idiopática.

DESCRITORES: Doença de Parkinson; Deglutição; Disfagia; Levodopa

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