

# Dysphagia as a Drug Side Effect

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## Abstract

### INTRODUCTION

Dysphagia is related to the impairment of food passage from the mouth to the stomach. Globus pharyngis implies the frequent and often painful sensation of a lump in the throat that usually does not interfere with swallowing and may even be relieved by food intake. The diagnosis is based upon a careful history, clinical examination, endoscopy, dynamic imaging (videofluoroscopy, cinematography, videonography [14]) and electrophysiologic procedures (including pharyngoesophageal manometry, electromyography and pH determinations) [15].

Structural lesions of the cervical spine such as diffuse idiopathic skeletal hyperostosis are rare causes of dysphagia. Dysphagia following anterior cervical fusion as well as globus and dysphonia due to dysfunction of the vertebral joints are more likely. Symptoms with swallowing fluids indicate a neurogenic origin. Dyscoordinated swallowing, nasal reflux, dysphonia or general weakness may also occur. Chronic aspiration with respiratory compromise is the main consequence in a variety of neurological disorders as well as in cases of postsurgical dysphagia. Relaxation of the upper esophageal sphincter indicates coordinated muscle movement between the pharynx and esophagus. Dysfunction of the pharyngoesophageal segment may lead to cricopharyngeal achalasia. A dyskinetic sphincter commonly represents an extrapharyngeal cause: i.e., disease associated with gastroesophageal reflux. Disorders of the esophageal phase of deglutition can produce retrosternal pain, heartburn, regurgitation and vomiting, as well as laryngeal and respiratory signs. Esophageal motility disorders include lower achalasia, tumors, peptic strictures, inflammatory diseases, drug-induced ulcers, rings and webs [16]. Motility disorders present with aperistaltic, spontaneous contractions, diffuse esophagospasm, or a hypermotile esophagus. Gastroesophageal reflux with esophagitis must always be excluded, especially in patients with a globus sensation [17]. The multiple features of the appearance of the symptoms of

dysphagia and globus makes multidisciplinary approach necessary in order to establish a diagnosis and begin effective treatment.

The evaluation of a patient with symptoms of dysphagia involves two principal aspects: determining the functional level of swallowing ability and the etiology of the swallowing disorder. In long-term care facilities, patients generally present with dysphagia symptoms related to established chronic medical conditions. Whether new symptoms of swallowing dysfunction are caused by an emerging medical problem or by progression of a previously identified disease process is a secondary issue in the long-term care environment; the crucial questions relate to quality of life, requirements for daily nutrition and care, and establishing appropriate levels of medical intervention.

The essential clinical issue for dysphagic patients in chronic care is the level of swallowing ability as it relates to the risk of aspiration and maintaining adequate nutrition and hydration. Evaluation of swallowing competence is further refined based upon related or unrelated medical conditions, patient and family requests, cognitive function and patient cooperation. The swallowing evaluation itself, and the impact of these other factors on decisions about the patient's swallowing safety, are defined as the functional diagnosis of swallowing.

Dysphagia describes the disability or problems in swallowing a wet or dry bolus properly and is normally associated with an impaired transport of the bolus. Dysphagia can be accompanied by a pain sensation in the chest mostly caused by impaction of the food bolus in the esophagus. Odynophagia describes only the status of painful swallowing without an impairment of the swallow and transport function. Dysphagia is a common clinical symptom in patients with reduced perception of the pharyngeal mucosa which leads to a subjective impairment of swallowing. If it is caused by complication of the therapeutic

action of a drug, dysphagia may also be because of viral or fungal esophagitis in patients treated with immunosuppressive drugs or cancer therapeutic agents, or antibiotics and immunological reactions to certain drugs such as erythema exsudativa multiforme or Stevens-Johnson syndrome. In the clinical diagnosis the drug history is crucial in order to identify causes of dysphagia secondary to side effects or complications of drug treatment. The following summary discusses the various mechanisms and causes by which drug treatment can lead to dysphagia in patients. Three major mechanisms have to be considered:

- dysphagia as a normal drug side effect,
- dysphagia as a complication of the drug actions, or
- dysphagia because of medication-induced esophagitis.

### **PATHOGENESIS OF DRUG-INDUCED DYSPHAGIA**

The smooth and striated muscle function of the esophagus can be influenced by a variety of drugs. The cholinergic muscarinic innervation is of importance for the coordinated function of the smooth muscle portion of the esophagus. Substances that affect muscle tone and activity can be either inhibitory or excitatory. So the inhibitory drug effects on esophageal motility play a role in reflux disease, which can subsequently cause dysphagia. The modification of the lower esophageal sphincter pressure (LESP) by hormones, drugs, food such as chocolate and peppermint, and liquids such as coffee and alcohol is an important pathogenetic mechanism, which causes gastroesophageal reflux disease by decreasing the LESP.

Drugs affecting the striated muscle portion of the esophagus act mostly via the central nervous system; these substances include sedative and narcotic agents. A direct effect on the striated muscle can be caused by muscle relaxants such as pancuronium or succinylcholine, generally used in anesthesia or intensive care units.

### **NEUROLEPTIC DRUG THERAPY**

Dysphagia can be a well-known side effect during antipsychotic or neuroleptic therapy. The dysphagia is mostly due to extrapyramidal motor disturbances which can lead to severe impaired function of the striated muscle of the oropharynx and the esophagus [1, 2]. Huges et al. [20] reported a case of a severe dysphagia complicated by weight loss and aspiration because treating a patient with haloperidol.

Among these complications of neuroleptic therapy, the most serious and potentially fatal complication is the neuroleptic malignant syndrome, which is characterized by extreme hyperthermia and skeletal muscle rigidity, causing dyspnea, dysphagia, and rhabdomyolysis [3]

As a new therapeutic strategy, local injections of botulinum-A toxin are increasingly used in patients with focal dystonia, such as idiopathic spasmodic torticollis, blepharospasm, or hemifacial spasm. In these patients, dysphagia due to the effect of the injected botulinum-toxin on the upper pharyngeal muscles is the most troublesome side effect.

### **LOCAL ANESTHETICS**

Local anesthesia of the oropharynx is commonly used for nasogastric tube insertion, upper gastrointestinal tract endoscopy, and esopharyngeal or dental manipulation. The local anesthetics can either be applied topically or injected to block afferent nerve conduction. The loss of sensory afferent input gives rise to a feeling of impaired or uncontrolled swallowing. This can be experienced or interpreted by the patient as dysphagia and can be extremely anxiety provoking unless explained beforehand to the patient.

### **DRUG-INDUCED XEROSTOMIA**

Xerostomia is a common side effect of a large number of commonly used drugs. Dysphagia due to xerostomia can be caused by two general mechanisms. First, the dryness of the mouth can lead to impaired oropharyngeal bolus transport, giving the patient the feeling of impaired swallowing. This form of dysphagia is usually easy to detect by taking a careful clinical history. Second, a causal link between xerostomia as a valid indicator of salivary gland hypofunction and esophagitis has been suggested. After acid reflux, clearance of acid from the esophagus is an important defense mechanism against the development of esophagitis. Acid neutralization by swallowed saliva is responsible for the stepwise increase in esophageal pH that occurs during acid clearance. First, virtually all acid volume is emptied from the esophagus by one or two peristaltic sequences, leaving a minimal amount of acid that sustains a low pH. Second, residual acid is neutralized by swallowed saliva. In patients with chronic xerostomia, an important defense mechanism has been weakened, leading to defective neutralization of acid, which increases the likelihood of injury.

### **ALCOHOL**

Both acute and chronic alcohol consumption may cause

esophageal dysmotility. Acute alcohol intake decreases LES and inhibits lower esophageal sphincter (LES) relaxation. This inhibitory effect of acute alcohol on LES is significantly reduced in chronic alcoholics, indicating the development of tolerance. Ethanol decreases esophageal contraction amplitude (ECA) and prolongs duration of contractions but has no effect on the velocity of esophageal contraction. Venous infusion of alcohol returned ECA toward normal values in alcoholics in withdrawal. Withdrawal of alcohol in chronic-dependent alcoholics caused esophageal dysmotility in more than 75 % of the patients with increased esophageal contraction amplitudes similar to Nutcracker esophagus or hypertensive LES-tonus. This suggests the development of a compensatory mechanism in chronic alcoholics leading to high pressure esophageal contractions during withdrawal. The underlying mechanism is not yet clear.

### DYSPHAGIA AS A COMPLICATION OF DRUG ACTION

Cancer therapeutic agents, mostly cytotoxic agents, act in two different ways. First, by predisposing patients to viral and fungal infections of the esophagus, and secondly by causing an esophagitis in which no infectious agent can be identified. It is hypothesized that in these cases the cytotoxic agents may injure the esophageal mucosa directly.

The predisposition to infectious cause of esophagitis is based on the immunosuppressant effect of cancer therapeutic agents. The most common opportunistic infectious agents are candidiasis [21] and herpes virus infection. Esophageal candidiasis is usually associated with an impairment of the immune system, as well as with local lesions (plaques, erosions, spasm) of the esophagus leading to esophagitis. It has also been reported as a complication of antibiotic therapy, especially with long-term treatment [4]. In recent years, candida esophagitis has gained further attention because of its association with AIDS, for which it constitutes a diagnostic criterion [5]. The typical clinical presentation is odynophagia, dysphagia, or retrosternal pain, although asymptomatic forms are frequent. The association of esophageal candidiasis with oropharyngeal candidiasis is variable, and absence of oropharyngeal candidiasis does not exclude esophageal involvement. Radiological appearances are pathognomonic, such that endoscopy is usually not necessary prior to treatment. Other forms of infectious esophagitis have to be considered in the differential diagnosis of dysphagia due to cytotoxic agents, particularly esophagitis caused by herpes and cytomegalovirus [14, 7].

Upper endoscopy is the diagnostic technique of choice, since it permits samples to be taken for histological and cytological study and cultures.

### ALLERGIC COMPLICATIONS CAUSING MUCOSAL LESIONS

Dysphagia can also be caused by mucosal defects due to systemic allergic skin reactions, such as the Stevens-Johnson syndrome. This syndrome, producing bullous inflammatory lesions of the skin and mucous membranes, may also involve the esophagus, thus causing dysphagia. Esophageal stricture may also occur as a late complication [8]. Sulfa-containing drugs have been implicated in up to 60 % of cases of Stevens-Johnson syndrome or erythema multiforme major. The diagnosis is usually based on the characteristic clinical findings of these diseases.

### DRUG-INDUCED ESOPHAGEAL INJURY

Drug-induced esophageal injury (DIEI) was first described in 1970 by Pemberton and extensively reviewed in the literature by Kikendall and Bott [9]. DIEI is usually caused by local irritation of the esophageal mucosa by orally ingested drugs.

The clinical presentation is characteristic in most patients with DIEI. There is a sudden onset of dysphagia (20 %), accompanied by retrosternal chest pain (72 %) or odynophagia (74 %) within 4 – 12 hrs after ingestion of the drug [9, 10]. However, sometimes the association with drugs is not identified initially.

The most common site of esophageal injury is near the level of the aortic arch, an area characterized by external compression from the arch itself, transition from skeletal to smooth muscle, and by physiological reduction in the amplitude of the esophageal peristaltic wave. The caustic potential of a variety of drugs has been demonstrated by placing the pills directly in contact with buccal or esophageal mucosa.

Acid producing substances with a pH less than 3 (e.g. doxycycline, tetracycline, ascorbic acid, ferrous sulfate), and slow-release emepronium bromide (anticholinergic drug employed to relieve urinary frequency) produce a moderate to severe injury of the mucosal layer. Actually two cases of esophageal ulceration because of intake of doxycycline used for malaria chemoprophylaxis were reported [18]. Some studies have shown that weak concentrations of hydrogen ion with prolonged exposure cause a comparable degree of mucosal damage to high concentrations of hydrogen ion, so

that all acid-producing substances are caustic with a more or less prolonged esophageal mucosal contact.

Other drugs including clindamycin, quinidine, potassium chloride, and standard emepromium bromide tablets reported did not produce acid solutions. There are several studies that suggest that acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with esophagitis or esophageal stricture formation, including low-dose ASA and over-the-counter NSAIDs [16].

The following findings explain the pathophysiologic of mechanisms of injury by drugs:

The prolonged contact of drugs leads to a high local concentration of the swallowed tablet and causes a compartment with increased osmolarity, leading to mucosal desiccation and damage, the dissolution rate of certain tablets might be too high, causing pathological drug concentrations or local development of heat.

**Figure 1**

Table 1: Effects on smooth muscle function

Inhibitory	Excitatory
Anticholinergic	Cholinergic agonists (ACH-esterase inhibitors, carbachol etc.)
Tricyclic antidepressant	Prokinetics (cisapride, metoclopramide)
Theophylline	
Ca <sup>2+</sup> -channel blockers	
Alcohol	

**Figure 2**

Table 2: Drugs and hormones that decrease the lower esophageal sphincter pressure

Cholecystokinin	Sekretin
Progesterone	Glucagon
Neurotensin	Vasoactive intestinal polypeptide
Dopamine	Calcitonin gene related peptide
Atropine	Butylscopolamine
Theophylline	Nitrates
Dopamin	Calcium antagonists
Alcohol	Fat
Chocolate	

**Figure 3**

Table 3: Drugs that cause xerostomia

Alpha-Sympathomimetics	Methyldopa
Analgetics, central	e.g. Codein, Dihydrocodein, Hydrocodon, Morphin, Pethidin, Fentanyl, Pentazocin, Levomethadon, Tramadol, Tilidin, Naloxon
Antiarrhythmics	Mexiletin, Ipratropiumbromid, Dilsopyramid
Antibiotics	Penicilline
Anticholinergic agents	Atropine (side effect even in local application), N-butylscopolamin, Scopolamin, Pirenzepin
Antiepileptic agents	Phenytoin
Antihistaminic drugs	e.g. Astemizol
Antihypertensive agents	Beta blocker, ACE-inhibitors (e.g. Captopril), Guanethidin, Clonidin, Alpha-1-blocker, Reserpin
Antitussive agents	Hydrocodon
Diuretics	loop diuretics, Thiazid derivates, Triamteren, Xipamid
Acidity blockers	
Muscle relaxant	Baclofen
Psychopharmaceutics	Benzodiazepine, Imipramin, Lithium salt, neuroleptics (derivates of Phenothiazin, Thioxanthen, Azaphenothiazin, Butyrophenon), Doxepin, tri- and tetracyclic antidepressive drugs
Vasodilators	Cinnarizin

**Figure 4**

Table 4: Drug-induced esophageal injury

Predisposing factors
Bedtime medications
Drug intake without sufficient fluid
Pill size
Left atrial enlargement
Thoracic surgery
Elderly patients
Esophageal motility disorders

Figure 5

Table 5: Pathogenesis of drug-induced esophageal injury

Changes in esophageal pH
Hyperosmotic effect of a prolonged contact of high local concentrations of a potentially caustic drug
Gastroesophageal reflux
Dissolution rate

Figure 6

Table 6: List of drugs implicated in esophageal injury

Antibiotics (doxycycline, tetracycline, clindamycin, oxytetracycline, minocycline, apocillin, erythromycin, phenoxymethylpenicillin, lincomycin, tinidazole)
Alprenolol chloride
Ascorbic acid
Aspirin, codeine, phenacetine combination
Aspirin alone
Emepronium bromide
Ferrous sulfate or succinate
Ibuprofen
Indomethacin
Phenylbutazone, prednisone
Potassium chloride
Quinidine
Theophylline

**CONCLUSION**

Most patients with medication-induced esophageal injury have no apparent abnormality of esophageal transit, and prior esophageal disease is not a prerequisite for its development. A variety of parameters have to be considered which influence the passage of drugs such as intake of fluid, body position of the swallowing patient, capsule size, and age of the patient.

In a study the transit time of drugs through the esophagus in normal individuals who were asked to swallow a small round barium sulfate tablet was investigated [12]. The authors showed that this tablet, similar in size and shape to aspirin, can remain in the esophagus for up to 90 min after ingestion, if the individual remained supine during the whole period. When swallowing small round tablets, the transit of these tablets can be transiently held up at the upper esophageal sphincter, the aortic arch, and distal esophagus immediately proximal to the lower esophageal sphincter. the risk of development of DIEI is enhanced by swallowing drugs in the supine position prior to sleeping [9]. In addition, swallowing decreases during sleep, diminishing the frequency of peristalsis as well as the ability of saliva to dilute medications present in the esophagus and to neutralize acidic substances. In more than 50 % of supine normal subjects, emptying of capsules into the stomach, taken with or without water, remained in the esophagus for longer than 10 min. Even capsules taken in upright position are rapidly cleared only if taken with water. Therefore, patients who take pills at bedtime without enough fluid intake are particularly at risk of developing DIEI as esophageal retention is then encouraged. Another risk factor predisposing for DIEI is external compression of the esophagus, due either to valvular heart disease with left atrial enlargement [11], or to esophageal entrapment by fixed mediastinal structures and adhesions following thoracic surgery [1].

The size and shape of capsules and tablets also seem to be contributing factors for the development of MIEI. Large (2 cm) oval and round tablets are delayed more than smaller (1 cm) oval and round tablets taken with or without water. For patients swallowing medications in the upright position, the quantity of water is not a significant factor for transit time of smaller preparations, but delay occurred when larger tablets were swallowed with small quantities of water. The esophageal transit of capsules was not affected by the volume of water. In the supine position, the smaller capsule was slower to transit than the larger [12]. In a questionnaire study from a general practice 6.158 questionnaires were received from patients [19]. 26 % said they had problems in swallowing tablets. A prominent complaint was the size of the tablet, followed by the surface, form and taste of the tablet. Twice as many women as men experienced swallowing problems.

Particularly at risk are elderly patients. First, they consume more medications; secondly, older patients are more likely to

have anatomic or motility abnormalities of the esophagus; and they are more likely to have cardiac enlargement with concomitant compression of the midesophagus. Motility problems in the elderly may be related to diabetes mellitus, autonomic neuropathy, swallowing dysfunction because of cerebral stroke, or connective tissue disease. Finally, decreased saliva production with age is responsible for decreased esophageal lubrication and increased likelihood of adherence of the drug to the esophageal mucosa. Furthermore, the salivary bicarbonate may play an important role in neutralizing residues of tablets with an acid pH [13].

To achieve good compliance and optimal pharmacotherapy, it is important for medical practitioners and pharmaceutical personnel to select the correctly formulated drug for their patients. Novel drug formulations, such as tablets that dissolve in seconds on the tongue without water, may alleviate the problem of swallowing tablets, and enhance the potential for improved compliance in patients who experience difficulty in taking tablets.

### CORRESPONDENCE TO

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