

*GENERAL ARTICLE*

## **DRUG-INDUCED OESOPHAGEAL LESIONS**

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### SUMMARY

Drugs reported to cause oesophageal problems-i.e. ulceration, stricture or obstruction are reviewed. Medicines that remain in or adhere to the oesophageal wall will cause injuries. The incidence of retention of solid medications in the oesophagus is double in patients with oesophageal abnormality. The medicine should be taken with adequate amount of water, not in supine position or just before bedtime. This adverse effect can be reduced by both the development of safer dosage forms and providing the appropriate informations about drugs and their uses.

Accidental ingestion of corrosives was for a long time recognized as the only possibility of damaging the oesophagus. But now, there is a long list of quite commonly used drugs that cause severe ulceration or stricture of the oesophagus in many patients. Simply because these drugs were swallowed without a sufficient amount of water and, generally, immediately before bed rest. When an irritant medication is held up in the oesophagus, oesophagitis develops which may progress to oesophageal ulceration and even stricture. The presenting symptoms are dysphagia and pain, usually retrosternal and often severe. Deaths have occurred from perforation or hemorrhage. Not only the chemical and pharmaceutical properties of the drugs themselves that are responsible for these injuries but also other factors such as postures of patients and drinking volumes of liquid.

### DRUGS WHICH CAUSE OESOPHAGEAL PROBLEMS

In recent years there have been many case reports concerning drug-induced oesophageal ulceration, stricture or obstruction in human. This suggests that the problem is serious and more common than is generally thought by doctors, pharmacists or patients.

Drugs that have been reported to cause oesophageal problems during these few years are reviewed.

#### 1. Bulk Laxatives

The bulk laxatives may easily cause obstruction to the oesophagus if they are not taken with an adequate amount of water. Three cases had been reported. The first patient took 2 teaspoons of Normacol, a combination of hygroscopic Karaya gum, with little water (1). The other two cases were caused by Angiolax, a hydrophilic gum laxative, in which its volume increased about 7 folds after the addition of water (2). The gum formed a clump in the oesophagus and caused symptoms of obstruction. The clump adhered so firmly that it could neither be pushed into the stomach nor removed by suction or snare.

So, the instruction for the administration of hydrophilic gum laxative should emphasize the importance of mixing an adequate amount of water with the preparation before taking.

#### 2. Co-trimoxazole

Bjarnason and Bjornsson (3) reported a case of a patient who developed oesophageal ulceration after ingestion of 2 tablets of co-trimoxazole without food or water. They concluded that co-trimoxazole was the cause of the patient's illness. The ulceration might possibly be regarded as a nonspecific reaction to the tablets, since the drug had no anticholinergic effects and the pH of 1 tablet in 2 millilitres of water was 6.

### 3. Emepromium Bromide

One of the most troublesome drugs that cause oesophageal ulceration is emepromium bromide. There were many case reports of this drug; all patients took the tablets with little water in the late evening (4-9). Ulcer formation was thought to be due to the prolonged passage time and locally damaging effect of the hygroscopic compound in the tablet. Anticholinergic effect of the drug also caused dry mouth which promoted adherence of the tablet to the oesophagus when swallowed with too little water.

### 4. Indomethacin

A non-steroidal anti-inflammatory drug, indomethacin, was also reported as a causative agent for oesophageal ulceration and stricture but the incidence was not common (10,11). The mechanism of injury was unknown. But in case of acid-induced oesophageal injury in patient with low oesophageal sphinctor pressure, indomethacin treatment resulted in more rapid healing of the inflammation (12). The possible reason was that prostaglandins played an important role in the pathogenesis of acid-induced oesophagitis and indomethacin inhibited the synthesis of these compounds.

### 5. Liquid Caustic

Cello et al (13) reviewed 17 patients who ingested household liquid caustic i.e. Drano, ammonium solution and liquid bleaching. The endoscopy revealed severe mucosal injury which varied from asymptomatic state to stricture formation or even death.

### 6. Naftidrofuryl

The oesophageal ulceration caused by naftidrofuryl in one patient was reported (14). The patient swallowed an evening capsule without water, 3 hours later developed a retrosternal pain radiated to the neck, back and epigastrium. Endoscopy confirmed a mild oesophageal lesion at a particularly vulnerable site.

### 7. Phenobarbitone

Walsh and Kneafsey reported a case of a patient taken phenobarbitone without water and produced oesophageal injury (15). The saturated solution of phenobarbitone in water is acidic in nature. They concluded that the tablets should be swallowed with water or dissolved first, particularly in patients with pre-existing oesophageal disease who were more liable to oesophageal injury from swallowing drugs.

### 8. Potassium Chloride

The wax-matrix slow-release potassium chloride tablet was introduced into the market to replace the enteric coated one that produced intestinal ulceration, hemorrhage, obstruction or even death (16). Although this product was considered to be safe, gastrointestinal complications such as ulceration, hemorrhage, obstruction and stricture were reported (16-18). These complications occurred particularly when there was a delay in gastrointestinal transit such as narrowing of the oesophagus by cardiac enlargement.

### 9. Quinidine

Five cases of quinidine-induced oesophagitis were reported in 1980-1981 (19,20). These patients took quinidine with little water and this probably permitted them to remain in the oesophagus producing local irritation. The drug itself is also a corrosive agent.

### 10. Tetracycline / Doxycycline

Although it has been known and warned for years that tetracycline and doxycycline could potentially cause oesophageal ulcer, more than 20 cases were published in these few years concerning this problem (21-26). The patients took one or more capsules without or with little water just before bedtime. Prolonged retention of the capsules in the oesophagus was thought to cause mucosal damage which was enhanced by a highly acidic pH of its aqueous solution (23).

## 11. Alcoholic Beverages

Clinical observations, experimental data and epidemiological studies suggested that there was a causal relationship between alcoholic abuse and oesophagitis as well as oesophageal carcinoma (27). The reason was that alcoholic beverages were still almost undiluted when passing through the oral cavity and oesophagus. With regard to the mechanisms of injury, alcohol may exert its effects directly by aggressive damage of the mucosa or indirectly by an impairment of the defensive mechanism. Hence, oesophageal lesions developed rapidly and healed more slowly under the influence of alcohol.

## PATIENTS' FACTORS

### 1. Patients at Special Risk

Although the retention of tablets and capsules might occur in any patient, the incidence was found more than 2 folds in those with oesophageal abnormality (28,29). Some diseases such as hypertension and myocardial infarction which produced cardiac enlargement that narrowed the oesophagus (13) or hiatus hernia (29) would prolong the transit time of the drug from the oesophagus to the stomach. The increase in contact time between the oesophageal mucosa and irritating drugs such as quindine, potassium chloride, ferrous sulfate and tetracycline would result in local irritation, inflammation and then ulceration (30,31). It may be concluded that any form of oesophageal obstruction and motility disorder predisposed to oesophageal injury. However, age, sex, weight and body size had no influences on the oesophagus movement rate (32).

Patients should be reminded that the risk of oesophageal injury may always happen with any kind of tablets or capsules. They should take solid medications with adequate amount of fluid and not just before bedtime. Patients at high risk of oesophageal retention should avoid solid medications whenever possible.

## 2. Effects of Patients'Postures and Drinking Volume

Since 1950, Faber and Praetorius (33) showed that, for the most rapid absorption, tablets should be taken with an ample volume of liquid and the person in an upright position before lying down on his right side in order to increase the passage of the drug to the intestine. It was proved that peristalsis was greater with a wet swallow than with a dry swallow (34).

In reviewing of case reports of drug-induced oesophageal lesions, almost all the patients took the medicines without or with small amount of fluid and just before bedtime (1-27). Thus, the medicines remained in or adhered to the oesophagus and caused troubles. Especially patients with oesophageal reflux taking medicines in supine position will get oesophagitis more frequently than those who take the medicines in sitting position (35). It is recommended that patients should remain standing at least 90 seconds after taking capsules or tablets, and all preparations should be taken with at least 100 millilitres of water to ensure rapid transfer (37,38). Evenmore, increasing the water volume will enhance the absorption of a poorly soluble drug, thus maximizing its bioavailability (39).

## 3. Effects of Temperature

Since decreasing oesophageal movement will increase the risk of drug adherence to the oesophagus, one factor that affected the rate of peristaltic movement is temperature (40-45). It was shown by many experiments that cold liquid, in comparison to room temperature liquid, would decrease or abolish the peristaltic amplitude and prolong the contraction wave in the distal oesophagus. Hot water accelerated the response of the oesophagus in swallowing, while cold water often delayed the drugs in entering the stomach and tend to pool them in the distal oesophagus. Some patients developed chest pain after ingestion of cold liquid because of complete absence of motor activity in the body of the oesophagus (44,45). Sometimes patients prefer to drink cold rather than

warm water with their medicines so, they should be advised to take the medicines only with room temperature or warm water not with cold one which decreases the clearances of the medicines from the oesophagus.

#### FORMULATION FACTORS

##### 1. Capsules

In general, capsules are more likely to stick and dissolve in the oesophagus than tablets (29,31). Sometimes when a capsule is swallowed without water it can remain in the oesophagus for up to 2 hours without noticing of any sensation (36). Hard gelatin capsules absorb water and become adherent to the moist mucosa of the oesophagus if their passage is delayed for longer than 2 minutes (37), then their disintegration will produce local irritation. It is suggested that capsules should be swallowed only after a lubricating water bolus, then taken with water and followed by a water chaser (46).

Pivampicillin was originally formulated in capsules which caused intestinal bleeding and erosion of gastric mucous membrane. No such reactions were observed in pivampicillin tablets (47). It was assumed that when tablets disintegrated, the contents spread rapidly over a large area, whilst capsules settled down on the mucous membrane and released their contents over a limited area with subsequent risk of local irritation.

##### 2. Tablets

All tablets nowadays are formulated to disintegrate rapidly when contact with water. This is achieved by incorporating swelling agents that need a small amount of water to exhibit their effects. When a tablet is swallowed with too little water, the hygroscopicity of the tablet can cause it to stick to the oesophageal mucosa resulting in local irritation and ulceration. Coating tablets with film which is less adhesive and water resistant will reduce the adhesion of tablets to the

oesophageal mucosa (31).

The slow-release wax-matrix formulation of potassium chloride will provide high concentration of drug ions which cause local irritation, especially when there is an impaired gut motility. The reformulation microencapsulated potassium chloride is widely dispersed, thus minimizes the irritation of mucosal lining (15).

Oval tablets are easier to swallow than the round ones, especially when they are big; and coated tablets are easier to swallow than uncoated ones (38).

Marvola et al (48) developed a method to measure the force needed to detach the drug from the oesophagus which may be useful in the formulation of products. By this method, it was shown that the force needed to dislodge a size 4 capsule in the oesophagus is 12 times higher than a sugar coated tablet. The force needed for an uncoated tablet is more than those for the film coated and sugar coated respectively (49).

#### CONCLUSION

Problems of oesophageal lesions after oral intake of certain drug formulations are a form of drug-induced disease. Prevention of this adverse effect can be done by both the development of safer dosage forms with less tendency to adhere to the oesophageal mucosa and providing the information about drugs and their uses. Patients should be advised to take their medicines with an adequate amount of water, not in supine position and not just before bedtime.

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