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Drug-Induced Oesophageal Disorders

Pathogenesis, Incidence, Prevention and Management

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Contents

Abstract

Drug-induced injury of the oesophagus is a common cause of oesophageal complaints. 'Pill-induced' oesophagitis is associated with the ingestion of certain drugs and accounts for many cases of erosive oesophagitis. To date, more than 70 drugs have been reported to induce oesophageal disorders. Antibacterials such as doxycycline, tetracycline and clindamycin are the offending agents in more than 50% of cases. Other commonly prescribed drugs that cause oesophageal injury include aspirin (acetylsalicylic acid), potassium chloride, ferrous sulfate, quinidine, alprenolol and various steroidal and nonsteroidal anti-inflammatory agents. However, many physicians and even more patients are not aware of this problem.

Capsules or tablets are commonly delayed in their passage through the oesophagus. Highly caustic coatings, direct medication injury and poor oesophageal clearance of pills can lead to acute inflammation. Oesophageal damage occurs when the caustic contents of a drug remain in the oesophagus long enough to produce mucosal lesions. Taking medications at bedtime or without fluids is a common cause of oesophagitis.

The possibility of drug-related damage should be suspected in all cases of oesophagitis, chest pain and dysphagia. History and gastrointestinal endoscopy will confirm the diagnosis. Treatment is supportive, although acid reduction is used frequently as an adjunct. This review reflects the current state of knowledge in this field.

Drug-induced oesophageal disorders (DIOD) are a common clinical problem.[1-16] The first report of oesophageal injury caused by drugs was published in 1970,[17] but DIOD is still widely unknown. In all cases of dysphagia and odynophagia without prior oesophageal symptoms, the possibility of DIOD should be suspected. Most patients who experience DIOD have no detectable oesophageal disorder, neither neuromotor nor obstructive.[3] Therefore, the major responsibility for such injury seems to depend primarily on the chemical content and formulation of the drug, the manner in which the drug is taken by the patient, the duration of mucosal contact and, to a lesser degree, anatomical and functional variables in the oesophagus.[1] The important publications on this topic accumulated during the past few years are reviewed here; they were identified via a literature search on Medline.

1. Incidence and Pathogenesis

The 2 major functions of the oesophagus are the transport of the food bolus from the mouth to the stomach and the prevention of retrograde flow of gastrointestinal contents.[18] The transport function is achieved by peristaltic contractions. Retrograde flow is prevented by the 2 oesophageal sphincters, which remain closed between swallows.

A number of drugs act directly on the smooth muscle of the lower oesophageal sphincter to reduce resting sphincter pressure in normal persons and in patients with achalasia.[19] Anticholinergics,[20] amyl nitrate, sublingual nitroglycerin (glyceryl trinitrate), theophylline and β-agonists have been tried with inconsistent results in achalasia patients.[21,22] The most experience has been reported with isosorbide dinitrate and the calcium antagonists, particularly nifedipine.[22] The sublingual use of isosorbide dinitrate 5 to 10mg before meals has been shown to decrease mean resting lower oesophageal sphincter pressures by 66%, with relaxation usually lasting at least 90 minutes.[21] Calcium antagonists (diltiazem, nifedipine, verapamil) interfere with calcium uptake by smooth muscle cells, producing relaxation of the lower oesopha-

Table I. Major drugs responsible for drug-induced oesophageal disorders (DIOD). Drugs in each class are ordered by the frequency of reports of DIOD with that drug

Antibacterials
Doxycycline
Tetracycline
Oxytetracycline
Minocycline
Penicillins
Amoxicillin
Ampicillin
Pivmecillinam
Clindamycin
Trimethoprim
Erythromycin
Lincomycin
Tinidazole
Rifampicin (rifampin)
Nonsteroidal anti-inflammatory drugs (NSAIDs)[a]
Aspirin (acetylsalicylic acid)
Indomethacin
Piroxicam
Ibuprofen
Naproxen
Diclofenac
Other drugs
Potassium chloride
Quinidine
Alendronate
Calcium dobesilate
Ascorbic acid (vitamin C)
Ferrous sulfate
Glibenclamide (glyburide)
Mexiletine
Captopril
Nifedipine
Estramustine phosphate sodium
Theophylline
Diazepam
Emepronium bromide
Thiazinamium
Thioridazine
Alprenolol
Warfarin
Phenytoin
Phenobarbital (phenobarbitone)
Tryptophan
Clomethiazole
Naftidrofuryl

a All NSAIDs can cause DIOD.

geal sphincter as well as reducing the amplitude of peristaltic contractions in the body of the oesophagus.[22] After nifedipine 20mg sublingually, lower oesophageal sphincter pressure is reduced by 30 to 40%.[22]

There are few data on the incidence of DIOD. One published estimate is derived from a Swedish study showing an incidence of 4 cases per 100 000 population/year.[23] This may be underestimated and does not include subclinical, misdiagnosed or unreferred cases. Wright[24] found an incidence of medication-induced oesophagitis of 3.9/100 000.

The first case was reported by Pemberton in 1970, and concerned injury by oral potassium chloride.[17] To date, over 70 drugs are known to cause oesophageal lesions, the most common of which are listed in table I.[1-16]

Anyone who ingests caustic pills is at risk of DIOD, because a moderate delay in pill transit through the oesophagus is a common event, even in persons with normal oesophageal motility (table II). A sudden onset of odynophagia and mid-chest pain without prior oesophageal symptoms is typical; painless dysphagia is a rare condition.[1] Other symptoms include haematemesis, bodyweight loss or dysphagia due to stricture. Oesophago-gastroduodenoscopy is the technique of choice for detecting DIOD, but endoscopy is not indicated in every patient when the history is typical. Single-contrast or double-contrast radiography are less sensitive than endoscopy.[3]

Haematemesis due to DIOD is less common than gastroduodenal bleeding associated with non-steroidal anti-inflammatory drugs (NSAIDs). Only 4% of gastrointestinal bleeding in the elderly is due to ulcerative oesophagitis, and only rarely has pill-related haemorrhage been reported.[25] If pills are swallowed without water or while supine, a significant delay in transit is normal. In most cases the oesophageal injury is caused by prolonged contact with the drug contents, and drugs appear to produce their damaging effects by a direct action on the oesophageal wall.[1,2]

Table II. Factors contributing to drug-induced oesophageal disorders

Fasting condition
Recumbent position
Decreased production of saliva
Hyposialorrhoea (e.g. caused by anticholinergics)
Not enough fluid taken with medication
Duration of contact with mucosa
Pre-existing oesophageal disorders
Age
Polymedication

Table III. Pharmaceutical factors in the damaging effects of drugs on the oesophageal mucosa

Concentration of chemical substance
pH of chemical substance
Slow release formulations
Method of delivery (capsule or tablet)
Size of the capsule or tablet

Several pharmaceutical factors are important, such as the chemical formula, concentration of chemicals in the drug, the method of delivery (tablets or capsules), the duration of contact with mucosa, the pH of the drug and the size of the tablets (table III).[1,26-28] In addition to size, other characteristics of the drug formulation may predispose to injury. Gelatin capsules become sticky or adhesive during dissolution when taken with inadequate liquids or are otherwise delayed in transit. Capsules taken by upright, otherwise healthy, individuals are cleared normally from the oesophagus within 15 seconds only if taken with water. If capsules become lodged in the oesophagus they may be difficult to displace, even with repeated swallows of water. Carlborg and Densert[29] have shown that doxycycline capsules remain longer in the oesophagus 3 times as often as doxycycline tablets.

Several lines of evidence suggest that the oesophageal injury is indeed caused by prolonged contact with the pill contents. Clinical evidence includes the frequent occurrence of symptomatic injury after improper ingestion of pills and the frequent sensation that a pill has stuck in the oesophagus before the development of symptoms. Endoscopic evidence includes the occasional observation of pill fragments at the site of injury, the usually sharp demarcation of injury and the frequent localisation of injury to areas of the oesophagus

subject to compression by the aortic arch or enlarged left atrium. Experimental evidence includes the production of similar lesions by holding pills in contact with the oesophageal mucosa of experimental animals or the buccal mucosa of human volunteers.[3]

Most injured patients have no predisposing factor other than improper swallowing of pills. However, compression of the oesophagus by an enlarged left atrium or a dilated aorta, especially when the oesophagus is trapped in a retrocardiac location after cardiac surgery, predisposes to pill retention and injury.[1] Because potassium chloride and quinidine pills, which are particularly caustic, are often prescribed for such patients, it is not surprising that many severe and complicated injuries have occurred in this setting. Although delay in pill transit is necessary for the production of pill-induced injury, this alone is not sufficient. The pill contents must also be inherently caustic if injury is to occur. More than 70 different medications in pill form have been reported to cause direct oesophageal injury. The mechanism of injury may vary. Drugs such as doxycycline, tetracycline, ascorbic acid (vitamin C), ferrous sulphate and slow-release emepronium bromide produce a pH below 3.0 when dissolved in 10ml of water or saliva.[1] However, caustic pills such as clindamycin, potassium chloride and quinidine do not alter the pH when dissolved, so acidity does not explain all injuries. Medications such as doxycycline, NSAIDs and alprenolol are taken up by the oesophageal mucosa, suggesting that mucosal damage may be due to accumulation of toxic concentrations of drug within the mucosa itself. Other postulated mechanisms include production of local hyperosmolarity with potassium chloride and induction of reflux by theophylline and anticholinergic agents.[3] Atropinic drugs inducing hyposialorrhoea may result in DIOD in patients taking potentially injurious comedication.[1]

The predominance of elderly and women patients in DIOD is explained by the underlying disorders that require therapy with potentially injurious medications.[1] Older people receive more drugs, spend more time in the recumbent position, produce less saliva, and are more prone to forget administration instructions even when physicians have properly given them.

Oesophageal motility disorders predispose to pill retention and injury. Clinical disorders associated with oropharyngeal dysphagia are motility and neuromuscular disorders and local structural lesions. Patients with hypertensive and hypotensive upper oesophageal sphincter are predisposed to injury.[19] Patients with neurological diseases such as Parkinson's disease, multiple sclerosis or amyotrophic lateral sclerosis can experience DIOD.

Patients with scleroderma are also prone to DIOD.[30-32] The basic pathological process of scleroderma is primarily atrophy of the smooth muscle with subsequent replacement and fibrosis of the submucosa and muscularis. In the oesophagus, pathological changes are confined to the lower two-thirds (the smooth muscle portion) of the oesophagus, giving rise to diminished or absent muscle contractions in the distal oesophagus and incompetency of the lower oesophageal sphincter.[30,31] The clinical manifestations of oesophageal dysfunction in scleroderma are dysphagia and heartburn.[30,31] Gastro-oesophageal reflux disease (GORD) may be severe because of the loss of lower oesophageal sphincter competency in conjunction with poor oesophageal clearance. The prevalence of erosive oesophagitis may be as high as 60%, with some patients developing Barret's oesophagus and subsequent adenocarcinoma.[32] Invariably, patients with oesophagitis are those with underlying oesophageal motility disorders from their scleroderma. Dysphagia may result from the motor disturbance itself or from a stricture complicating reflux.[30,31]

2. Specific Drugs

2.1 Antibacterials

Antibacterials account for more than 60% of all reported cases of DIOD and top the list of medications.[1-4,6,33,34] Tetracycline and, particularly, dox-

ycycline appear to be the most common causes (table I).[35-38]

Tetracycline, an antibacterial of proven efficacy against many micro-organisms, continues to enjoy a great degree of popularity among physicians. Although certain adverse effects such as hepatic injury and discoloration of teeth in children have been popularised, very little has been written about another relatively common adverse effect, oesophagitis.[39] In a review by Kikendall[3] of pill-induced oesophageal injury, 26 different drugs were cited as causative agents in 221 cases. Of these 221 cases, tetracycline and its congeners were responsible for 109 cases. Additional cases of tetracycline-induced oesophagitis have been reported by Crowson et al.,[40] Schneider,[41] Channer and Stollanders[42] and Delpre.[43]

The clinical picture of doxycycline-induced oesophagitis is characterised by sudden onset of odynophagia and chest pain. The patients are frequently young women with no history of oesophageal dysfunction. The sequence of events suggests that the tablet remains lodged in the oesophagus, and this is encouraged by taking the tablet at night and without water.[34,44]

The exact mechanism of tetracycline-induced oesophagitis is not completely known. Three factors of variable importance in producing this condition are: (i) oesophageal transit time; (ii) the status of the oesophageal mucosa; and (iii) the biochemical and physical properties of the drug.[39] Evidence suggests that inflammation results from prolonged mucosal contact with the drug as a result of increased transit time. Well-known factors that affect transit time include luminal narrowing, the posture of the patient when swallowing, the amount of fluid taken along with the drug and various motility disorders. Common causes of luminal narrowing include tumours (intrinsic and extrinsic), cardiac enlargement, strictures, webs, rings and spasms.[39]

Posture plays a significant role in the transit time of pills, as demonstrated by Evans and Toberts.[45] The transit time of pills was markedly prolonged in individuals assuming the supine position compared to those sitting or standing. The volume of liquid ingested with the drug likewise influences transit time. In a study by Applegate et al.,[46] individuals who ingested pills with a greater volume of liquid had shorter transit time.

Well-characterised motility disorders such as achalasia and diffuse oesophageal spasms increase transit time by retarding the progression of oesophageal contents. Impaired motility may also be seen in patients with presbyoesophagus and diabetes mellitus. The ingestion of cold substances may also increase transit time. The relative importance of the oesophageal mucosal status remains in question. Perhaps this factor plays a more significant role in patients without any obvious oesophageal disorders. An inflamed mucosa may provide the appropriate milieu necessary for the drug to manifest its harmful effects. Severe mucosal inflammation may also produce oesophageal spasms, which may further increase transit time.[39]

Tetracycline is an acidic compound, which makes it potentially harmful to the oesophageal mucosa. Direct mucosal contact with the drug seems necessary, since no cases of oesophagitis have been reported with parenteral use. The physical form of the tetracycline also seems to play a role. Beel[39] reported that 7 out of 8 patients with drug-induced oesophagitis had taken tetracycline in the capsule form, which is probably more difficult to swallow than pill form. Interestingly, no cases of oesophagitis have been associated with the ingestion of liquid tetracycline. One explanation may be that the liquid form becomes diluted and partially neutralised with saliva.[39]

A diagnosis of tetracycline-induced DIOD should be strongly suggested by the temporal relationship of the ingestion of tetracycline and the onset of oesophageal symptoms. Being cognisant of this condition may avoid the necessity for an extensive diagnostic evaluation. However, oesophagoscopy is recommended if haematemesis occurs and if symptoms persist for an inordinate length of time.[39]

Fortunately, in most cases, tetracycline-induced DIOD is a self-limiting condition and no specific

treatment is generally required. With cessation of tetracycline ingestion, the symptoms usually abate within 2 to 6 days and pathological resolution occurs within 5 to 7 days. Antacids generally provide quick and effective relief of pain. Since reflux of gastric contents may further exacerbate the existing oesophagitis, proton pump inhibitors, H_2 antagonists or metoclopramide may prove useful. Occasionally, patients are unable to tolerate oral feeding and intravenous fluids may be required. No serious sequelae, such as strictures, have been reported.[39]

Other antibacterials that may cause injury are clindamycin, oxytetracycline, minocycline, penicillins, ampicillin, erythromycin, and pivmecillinam (table I).[3,47-49]

2.2 Nonsteroidal Anti-Inflammatory Drugs and Aspirin (Acetylsalicylic Acid)

NSAIDs can adversely affect every level of the gastrointestinal tract from the oesophagus through the stomach to the small and large intestines.[25] Although NSAIDs are a common cause of erosive gastritis and ulcers, it is not widely recognised that these drugs may induce oesophageal injury.[1] During the past 10 years, however, investigators have found that drug-induced oesophagitis is associated with the intake of all NSAIDs, including aspirin (acetylsalicylic acid), indomethacin, piroxicam and diclofenac (table I).[25,50-55]

A large variety of diseases treated by NSAIDs are associated with a significantly increased risk of oesophageal erosion or stricture; the risk appears similar for both of these.[51] GORD is a common condition that affects about one-third of the population at any given time. However, less than 5 to 10% of all patients with GORD develop erosive oesophagitis or oesophageal stricture.[52] The factors leading to the development of more severe forms of GORD are not well understood. Several studies based on relatively small numbers of patients have suggested a link between the ingestion of NSAIDs and the development of erosive oesophagitis as well as oesophageal stricture.[4,33,52,54,55]

More than one-third of the cases of NSAID-induced DIOD reported have been complicated by stricture or haemorrhage, some even having fatal outcomes.[53-55] NSAIDs account for about 8% of all reported cases of DIOD. Although NSAIDs do not frequently cause DIOD, severe bleeding may occur.[3]

Taha et al.[50] found that endoscopic oesophagitis is more commonly found in NSAID users with abdominal complaints. Histological oesophagitis is not essential for development of NSAID-related oesophageal damage and other mechanisms, such as direct toxicity, should be considered.

The mechanism of NSAID-related ulcerative oesophagitis is believed to be related to abnormalities in oesophageal motility and gastro-oesophageal reflux, both causing prolonged exposure of the mucosa to the NSAID. NSAIDs are acidic molecules with pKa values of 4 to 5. In the presence of gastro-oesophageal reflux, the pH of the distal oesophagus is less than 4 and the NSAID may enter the mucosal cell and exert a direct toxic effect.[25] Prolonged retention of tablets can occur if important factors in oesophageal clearance, including gravity, salivation and motility, are disturbed.[45,56] This is particularly important in elderly patients, who are more likely to be bedridden and to have abnormalities in salivation and in oesophageal motility. Women have twice the reported rate of drug-induced oesophageal injury as men.[4] In contrast to NSAID-induced gastritis, the role of prostaglandin inhibition on oesophageal cytoprotection is controversial and, most likely, only of minor significance.[1,3] Consequently, a direct toxic effect is the most likely mechanism of NSAID-induced oesophageal injury.[25]

NSAID use may be associated with the development of benign oesophageal strictures, especially in patients with gastro-oesophageal reflux, which may require endoscopic dilation.[53,54,57-59]

Levine et al.[53] found oesophageal strictures caused by ibuprofen tablets. In a case-control study in patients with GORD, oesophageal stricture was found in 49% of the 53 patients who took NSAIDs compared with 12% of the 165 controls who did

not.[58] In a second case-control study, 22 of 70 patients with benign oesophageal stricture consumed NSAIDs regularly, compared with 10 of 70 controls without stricture.[59] Lanas and Hirschowitz[60] described a significant association of NSAIDs and stricture. 62% of 55 patients with endoscopically verified oesophagitis had recent intake of either aspirin or other NSAIDs, compared with 26% of the 42 controls without oesophagitis.

Aspirin use emerged as an associated risk factor for oesophagitis[60] and oesophageal variceal bleeding. Lédinghen et al.[61] found that the use of aspirin was associated with high risk of a first episode of variceal bleeding, suggesting that patients with portal hypertension should avoid taking these drugs.

Wilcox et al.[62] reported aspirin and NSAID use by 9% of patients with variceal bleeding. The precise role of aspirin and NSAIDs in variceal bleeding remains to be determined, but the 2 main candidate mechanisms are erosion of the oesophageal mucosa through local irritation, and the inhibitory effect of these drugs on platelet aggregation. Aspirin has an irreversible antiplatelet effect, whereas other NSAIDs inhibit platelet aggregation only at a critical drug concentration. This could explain why the majority (90%) of cases who had used one of the drugs under study had taken aspirin.

A study by Talley et al.[51] suggests that aspirin and NSAIDs are linked to dyspepsia and heartburn in the elderly. However, a clear dose-response effect was not demonstrated.

Semble et al.[63] evaluated endoscopically 60 patients with rheumatoid arthritis who had taken NSAIDs over a 5-year period. 20% had evidence of erosive and/or ulcerative oesophagitis. Similarly, Sun et al.[64] studied a total of 140 patients with rheumatoid arthritis, of whom 122 were taking NSAIDs, by upper gastrointestinal series, with additional manometric studies and oesophagoscopy in the 66 patients who had been hospitalised. Lower oesophageal sphincter dysfunction with lower segment motor abnormalities were noted in about one-third of the 66 hospitalised patients, with 6 cases of oesophageal stenoses, 2 oesophageal ulcers and an unspecified number of cases of oesophagitis.

Patients with a hiatus hernia appear to be particularly at risk of developing oesophageal ulcers. Shallcross et al.[65] could demonstrate that patients receiving NSAIDs, especially those with a hiatus hernia, are at risk of oesophageal ulceration and presumably, subsequent stricture formation. Delay of passage of tablets into the stomach has been shown to be more common in patients with a hiatus hernia, and this may partly explain the association between hiatus hernia and oesophageal ulceration. This hypothesis is supported by occurrence of some ulcers on a background of histologically normal mucosa, suggesting very localised action. Oesophageal reflux, particularly in those with a hiatus hernia, would then more readily cause oesophageal damage. The authors suggest that NSAIDs should be prescribed with caution to those with a hiatus hernia and that endoscopic surveillance would be advisable in this group. In elderly patients who are prone to slow oesophageal emptying and may have impaired oesophageal clearing, the passage of NSAIDs may be slowed prior to stricture development, resulting in prolonged exposure of the oesophageal mucosa to the irritant action of the NSAID and stricture development.[64]

2.3 Alendronate

A new, and probably increasing, cause of oesophageal ulceration is alendronate (table I). Alendronate, an aminobisphosphonate used for the treatment of osteoporosis in postmenopausal women and Paget's disease of bone, can cause chemical oesophagitis with erosive lesions and severe ulceration.[66-68] Failure of alendronate tablets to pass though the oesophagus may result in prolonged local mucosal exposure to the drug. Endoscopic findings in patients with oesophagitis associated with alendronate were generally consistent with a chemical cause. Some patients also had erosive or ulcerative mucosal damage with exudative inflammation, accompanied by thickening of the oesophageal wall. Bleeding was rare and stomach or duodenal involvement unusual. In most of the

severe cases of oesophageal complications identified by post-marketing surveillance, recovery occurred when alendronate was stopped, with additional treatments including an acid-suppressing agent or sucralfate, or both, analgesia (local and systemic) and parenteral nutrition when necessary. Drug-induced acid suppression is not a substitute for the discontinuation of alendronate. Follow-up of patients for the possible development of oesophageal strictures is important.

De Groen et al.[66] reported on 3 patients in whom severe oesophagitis developed shortly after the start of treatment with alendronate. Graham et al.[67] found that alendronate causes mucosal injury to the upper gastrointestinal tract, similar to aspirin. A recent study by Lanza and Carlson[69] showed that alendronate therapy reduces the healing rate of aspirin-induced mucosal damage suggesting that, in light of these studies, it would not seem to be prudent to prescribe concomitant NSAIDs and alendronate without caution and close follow-up.

Alendronate and pamidronate, the other primary aminobisphosphonate that is associated with erosive oesophagitis, share the common property of containing an amino side chain, and it has been suggested that this may be responsible for development of erosive mucosal damage.[70-72] The presence of oesophageal damage suggests that alendronate is a topically corrosive drug. That alendronate is a recognised cause of pill-induced oesophageal damage when blood concentrations are low suggests that the injury is topical, similar to that seen with solid potassium chloride preparations.[67,73-75]

On the basis of the reported oesophageal adverse effects, the administration instructions for alendronate were revised worldwide, indicating that the drug should be taken when the patient is arising for the day with at least 200ml of water.[66] Previous experience with solid potassium chloride suggests that a change in formulation (e.g. microencapsulation) that prevents high local concentrations may allow this beneficial drug to be used safely. Graham et al.[67] evaluated the 40mg dose of alendronate. Additional studies to evaluate the 10mg dose are planned.[67]

2.4 Potassium Chloride

Potassium chloride pills can cause oesophageal haemorrhage and strictures, even with fatal results (table I).[3,17] This drug in some of its solid forms remains one of the most harmful substances when retained in a fixed location within the oesophagus.[76-79] Oesophageal symptoms should be promptly investigated in patients taking potassium chloride.

Potassium intake has contributed to the death of at least 6 patients.[3] Four patients taking slow-release potassium chloride tablets bled to death from oesophageal ulcers, 3 of which had penetrated the aorta, the left atrium or a bronchial collateral artery.[3] All of the patients who died and most of those in whom strictures developed have had either massive left atrial enlargement or lesser degrees of cardiomegaly combined with a history of cardiac surgery. These conditions favour pill retention.[57]

In contrast to the sudden development of chest pain after oral administration of antibacterials, most patients injured by potassium chloride present with progressive dysphagia and relatively little pain.[1] Most patients have been taking the potassium chloride pills for weeks, months or even years. As a result of the painless progression, the relationship of symptoms to the pills is often not noted until a densely fibrotic stricture has been produced. It is unclear why these pills do not produce the painful acute ulcers seen in patients injured by most other pills, but the absence of acute pain is probably an important factor permitting progression to stricture.[3]

Patients with significant cardiomegaly, particularly those who have undergone cardiac surgery, should avoid potassium chloride pills and other caustic pills.[76] If they cannot, they should take the pills while upright and should follow the pills with a full glass of water. Oesophageal symptoms should be promptly investigated in such patients.[3] Most cases of potassium chloride–induced oesophageal injury are caused by the wax-matrix, slow-release tablets that are widely prescribed today. Whether this formulation is more likely than other potassium chloride formulations to cause oesoph-

ageal injury is unknown, because the wax-matrix pills are much more widely prescribed than the other pill formulations.[3]

2.5 Quinidine

Quinidine may cause oesophagitis and oedema. 13 cases of pill-induced oesophageal injury have been reported in patients taking no caustic medication other than quinidine. In 7 of these patients, oesophageal strictures have developed.[3] Only 2 quinidine-injured patients had factors predisposing to pill entrapment and injury.[13,33,80,81] In patients with quinidine-induced oesophageal injury, profuse exudate and oedema tend to develop which on barium swallow may appear as a fixed, irregular filling defect suggestive of carcinoma.[81]

2.6 Other Medications

Other medication responsible for DIOD are emepronium bromide,[82-84] theophylline,[85,86] alprenolol,[87,88] captopril,[89] phenobarbital (phenobarbitone),[90] thiazinamium,[91] ascorbic acid[92] and ferrous sulfate.[93] Endoscopic treatment of bleeding oesophageal varices with sclerosing agents (polidocanol) can induce ulcerations and even perforation.[94-96]

3. Differential Diagnosis

A variety of other conditions than DIOD can be associated with the development of 1 or more discrete, superficial ulcers in the upper or mid-oesophagus.[97] Herpes oesophagitis should be the major consideration in the differential diagnosis of this finding.[98] In some patients, herpes oesophagitis can be indistinguishable from drug-induced oesophagitis on double-contrast studies. However, viral-induced ulcers tend to have a more widespread distribution than the ulcers associated with drug-induced oesophagitis. The clinical history is also helpful for differentiating these conditions, because patients with herpes oesophagitis are likely to be immunocompromised due to underlying malignancy or treatment with radiation or chemotherapy.[97] Occasionally, herpes oesophagitis can occur as an acute, self-limited disease in otherwise healthy patients who have no underlying immunological problems.[99] However, these patients usually present with a characteristic flu-like prodrome consisting of fever, headaches, myalgias and upper respiratory infection prior to the sudden onset of severe odynophagia.[99]

Reflux oesophagitis is a more common cause of shallow ulcers and erosions in the oesophagus. However, the ulcers of reflux oesophagitis are almost always located in the distal oesophagus, and there is often evidence of a hiatal hernia and gastro-oesophageal reflux at fluoroscopy. *Candida* oesophagitis can also cause ulceration, but the ulcers typically occur on a background of diffuse plaque formation, producing a characteristic 'shaggy' oesophagus.[100] Rarely, Crohn's disease can be manifested by small aphthous ulcers in the oesophagus, but these patients almost always have evidence of advanced Crohn's disease in the small bowel or colon.[101]

Giant oesophageal ulcers can also be caused by nasogastric intubation, endoscopic sclerotherapy, Crohn's disease, ulcerated oesophageal carcinomas and infection with HIV or cytomegalovirus (CMV). The correct diagnosis is usually suggested by the clinical history. Recently, giant oesophageal ulcers caused by HIV or CMV have been encountered with increasing frequency in HIV-positive patients with odynophagia.[102,103] The ulcers typically appear as giant flat lesions in the oesophagus. However, the possibility of HIV or CMV should be suspected when giant oesophageal ulcers are found in HIV-positive patients. Furthermore, Stevens-Johnson syndrome may involve the oesophagus with severe and bleeding oesophagitis.[104]

Drug-induced strictures usually appear as concentric areas of tapered narrowing in the mid-oesophagus. Other causes of mid-oesophageal strictures include Barrett's oesophagus, caustic ingestion, mediastinal irradiation, primary and metastatic tumours, and, rarely, oesophageal involvement of dermatological disorders such as epidermolysis bullosa dystrophia and benign mucous membrane pemphigoid. In most

cases, the correct diagnosis is apparent from the clinical history.[97]

4. Therapy and Management

Most uncomplicated cases of DIOD heal spontaneously, with resolution of symptoms in a few days to a few weeks.[1] The best treatment is removal of the offending drug, followed by supportive care (table IV). Parenteral or liquid oral analgesics may be required for a short time for the acute erosive types of damage. Avoidance of topically irritating foods (citrus fruits, alcohol) is helpful during the acute stages.[1] Besides sucralfate, there are no data from the literature that acid suppressive or antisecretory drugs play an active role in the healing process.[1]

Severe forms of DIOD may be treated with parenteral hydration or alimentation. Oesophageal haemorrhage is treated by therapeutic endoscopy; surgery may be required only in case of massive haemorrhage. Inflammatory strictures may resolve spontaneously, but chronic strictures will require endoscopic dilatation.[3]

Prevention includes education of patients in the proper methods for taking pills. All drugs should be swallowed with the patient in the upright position, followed immediately by at least 100ml of fluid (table V). Most instructions seem to be common sense advice, but in the case of alendronate the instructions have been objectively tested.[66] The patient should remain upright for 10 to 15 minutes after swallowing before lying down. If delayed transit of drugs through the oesophagus is possible because of motility dysfunction or diverticula, medications should be prescribed in liquid form or crushed and dispersed in fluid. Concerning the intake of alendronate, the instructions were revised worldwide on the basis of the analyses reported by de Groen et al.[66] Every physician must be aware of DIOD and of proper methods of taking drugs.[1,3]

Table IV. Treatment of drug-induced oesophageal disorders

Avoidance of offending drug/irritating food
Supportive care
Topical analgesics
Parenteral hydration/alimentation
Endoscopic dilation of stricture
Acid suppression
Antisecretory drugs

Table V. Prevention of drug-induced oesophageal disorders

Patient should ingest drug while in upright position
Drug should be taken with at least 100ml of fluid
Patient should remain upright for at least 15 minutes after swallowing
Preparation of drug in liquid or crushed form may aid passage through the oesophagus

Pinos et al.[105] used liquid sucralfate, based on a study by Pleet et al.[106] in which isotopically labelled sucralfate adhered to oesophageal ulcers. The symptoms were absent after the third day in 2 of the patients and after the fourth day in the patient who showed the most conspicuous lesions by endoscopy. None of the patients allowed a control gastroscopy.

5. Conclusions

DIOD has become an increasingly common condition. Most cases result from ingestion of tetracycline or doxycycline; other significant medications causing DIOD are potassium chloride, quinidine and NSAIDs. The diagnostic gold standard is endoscopy. The best treatment is removal of the offending drug, followed by supportive care. Guidelines for prevention of DIOD include intake of the drug with the patient in an upright position, followed by swallowing of an adequate amount of fluid.

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