Management of Biliary Colic

Reviewed by:
Dr Anil Ballani
MBBS, MD (internal Medicine)
Lilavati Hospital (Bandra) and
Hinduja Healthcare Surgical (Khar)
Mumbai

Overview

Biliary colic is the most common clinical presentation of symptomatic gallstone disease, and refers to acute biliary pain which occurs when the gallbladder contracts against any stone obstructing the cystic duct or common bile duct of the biliary tree. Patients with biliary colic usually complain of a sharp, steady or intermittent pain in the upper abdomen, mostly under the right side of the rib cage; it is frequently accompanied with nausea and vomiting.[1-4]

Epidemiology of Gallstones

It is estimated that almost 10% to 20% of adults have gallstones, of which 1% to 3% of patients are symptomatic and present with biliary colic. In developed nations, the prevalence of gallstone disease reportedly ranges from approximately 7.9% in men to 16.6% in women and in Asians, it ranges from approximately 3% to 15%.[2,5,6]

Gallstone disease is a multifactorial disease. In the general population, one of the main risk factors for developing gallstone disease is gender; gallstones are more common in women than in men.[6] Likewise, biliary colic has a female predominance due to the influence of estrogen on the formation of gallstones. Obesity and elevated cholesterol are also strongly correlated to biliary colic and gallstone disease.[2] Additional factors are age, genetics, rapid weight loss, glucose intolerance, insulin resistance, high dietary glycemic load, alcohol use, diabetes, drugs and pregnancy (Box 1).[6,7]

Etiology of Gallstones

Gallstones, which are the primary causative factor for biliary colic, are formed within the gallbladder and are composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials.

Box 1: Factors influencing gallstone disease

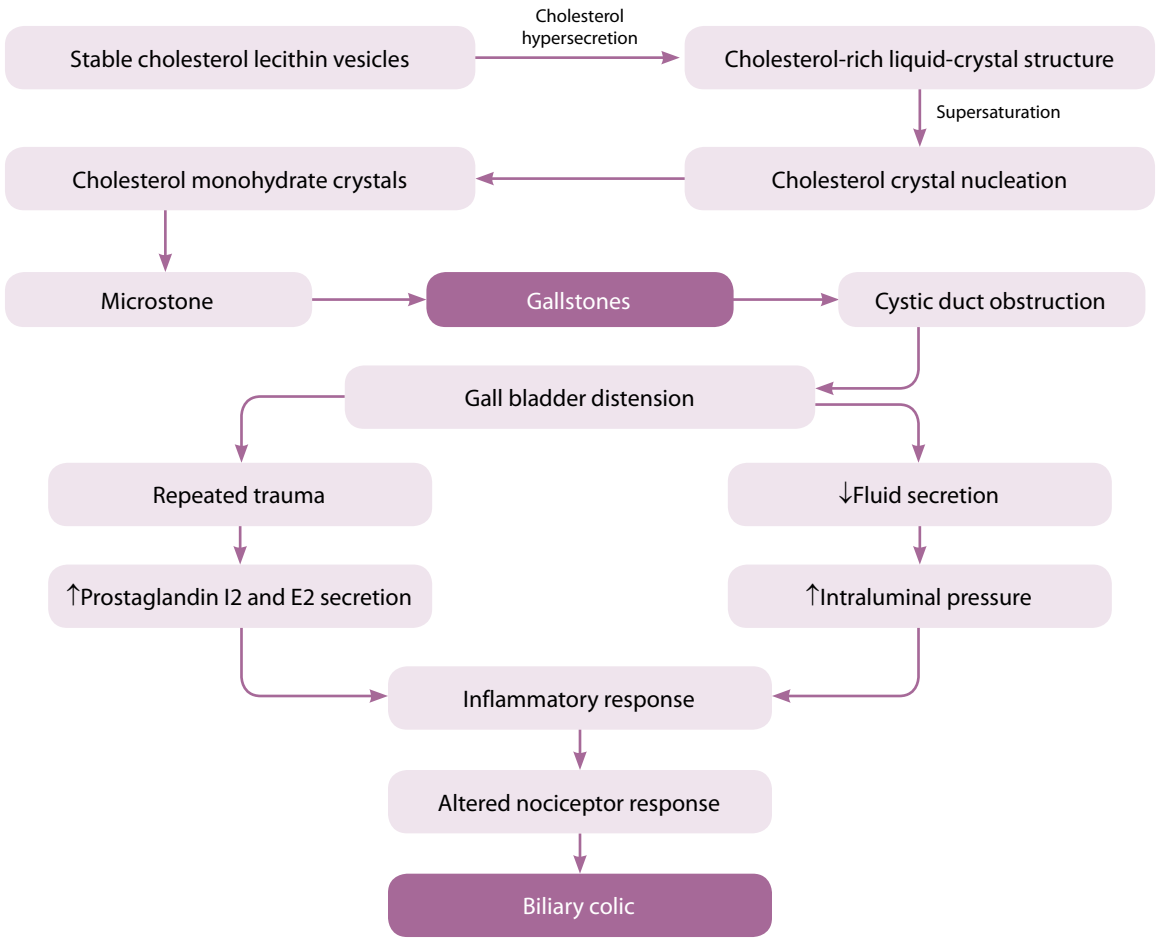
- Female gender
- Increasing age
- Genetics
- Obesity and body fat distribution
- Rapid weight loss
- Diet; increased intake of fat, refined carbohydrates and decrease in fiber content
- Alcohol use
- Pregnancy
- Physical inactivity
- Drugs
- Diabetes

The pathophysiology of gallstones is suggested to be multifactorial and probably develops from complex interactions between many genetic and environmental factors. Gallstones formation usually involves three steps: saturation, crystallization and growth. Unphysiological biliary supersaturation from hypersecretion of cholesterol, gallbladder hypomotility and the accumulation of mucin gel contribute to the formation of cholesterol gallstones.[2,6-8]

These stones may stay in the gallbladder and remain asymptomatic or may enter the cystic duct or common bile duct where they may become lodged and cause pain when the gallbladder contracts.[2] The obstruction in the cystic duct raises the intraluminal pressure within the gall bladder which together with cholesterol supersaturated bile, triggers an acute inflammatory response. Additionally, the trauma caused by the gall stones stimulates the synthesis of prostaglandin I2 and E2 which also mediates the inflammatory response.[9] Following the inflammatory response, a complex set of chemical signals alters the transduction properties of nociceptors, which then can be activated by low intensity or innocuous stimuli (Figure 1).[6,10]

Symptoms of biliary colic usually manifest after a large, fatty meal, since it triggers the digestive system's demand for bile leading to contraction of the gallbladder; in the event of a gallstone blocking the cystic duct or the common bile duct, the vigorous contraction of bile duct

Figure 1: Mechanistic approach to gallstone formation and biliary colic



to try to move the stone causes the typical pain of biliary colic.[1,2,11]

Evaluation in Patients with Biliary Colic

Patients with gallstone disease usually present with symptoms of biliary colic characterized by intermittent or recurrent episodes of constant, sharp, right upper quadrant (RUQ) abdominal pain.[2,5,7] The pain is visceral and radiates to the adjacent area which occurs due to the impaction of stone in the cystic duct or sphincter of Oddi. In about 60% of cases the pain is radiating to the angle of the right scapula or shoulder and to the retrosternal area in less than 10% of cases.[12] With uncomplicated biliary colic, patients most often present only with pain; however, some may also report nausea and/or vomiting. Fatty meals are a common trigger for gallbladder contraction. The pain usually starts within an hour after a fatty meal and is often described as intense and dull, and may last from 1 to 5 hours. Patients with biliary colic will generally only have RUQ or epigastric tenderness on physical exam with abdominal distension and rebound tenderness being less common. In an uncomplicated biliary colic, the patient is afebrile and has an essentially benign abdominal examination without rebound or guarding.[2,5]

Initial laboratory tests to evaluate gallstones often include a complete blood count and a metabolic panel with liver function tests. Stones within the gallbladder or cystic duct typically do not produce any laboratory abnormalities, whereas a stone or blockage in the common bile duct usually manifests with elevated liver enzymes.[2,5]

The three primary methods used to diagnose gallstone disease are ultrasonography, nuclear scanning (cholescintigraphy), and oral cholecystography. RUQ abdominal ultrasound remains the first line and best imaging modality to diagnose gallstones. Ultrasonography, with an estimated sensitivity of 84% and specificity of 99%, can detect stones as small as 2 mm in diameter. It

can reveal the presence of common-bile-duct stones, show bile-duct dilatation and detect thickening of the gallbladder wall. If an ultrasound study cannot explicitly rule out acute cholecystitis, then a nuclear medicine cholescintigraphy scan, also known as a HIDA scan can be performed, which are useful in evaluating acute or chronic cholecystitis and biliary dyskinesia. Abdominal CT is less sensitive than ultrasound at evaluating stones within the gallbladder.[2,5,7] Of late, magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) has emerged as an excellent imaging study for the noninvasive identification of gallstones anywhere in the biliary tract, including the common bile duct.[13]

Unlike the more commonly encountered condition of cholecystitis that is caused by a mechanical blockage of the cystic duct, acalculous cholecystitis is a form of cholecystitis caused by dysfunction or hypokinesis of gallbladder emptying. Gallbladder stasis, secondary to lack of gallbladder stimulation, leads to concentration of the bile salts with a build-up of pressure within the organ resulting in ischemia, pressure necrosis and perforation. It also increases seeding and growth of enteric pathogens such as *Escherichia coli*, Klebsiella, Pseudomonas, and *Enterococcus faecalis*.[14]

Individuals with chronic acalculous cholecystitis may have decreased function of gallbladder emptying, hypokinetic biliary dyskinesia. Chronic acalculous cholecystitis is treated the same as cholecystitis with stones. A laparoscopic cholecystectomy is the treatment of choice. Administration of broad-spectrum antibiotics is routinely done that would be effective in treating any systemic bacteremia.[14]

Management of Gallstones and Biliary Colic

Management of gallstones can be categorized into two groups: asymptomatic gallstones and symptomatic gallstones. Patients with asymptomatic gallstones require to be counseled as regards symptoms of biliary colic and when to seek medical attention. Patients with biliary colic do not necessarily require hospital admission. They may be treated symptomatically with a low-fat diet, oral or parenteral analgesia, and anti-emetics, and follow up for elective laparoscopic cholecystectomy as an outpatient within a reasonable time-frame. However, patients with severe or intractable abdominal pain will require hospital admission, more urgent surgical consult and intravenous antibiotics for symptomatic relief.[2,5]

Analgesia for Acute Attack of Biliary Colic: Use of Antispasmodics

The intensity of pain in biliary colic is generally high with a mean visual analogue scale of 9 cm on a 0-10 cm scale. Therefore, immediate medical attention and analgesia for pain management is mandatory. Depending on the acute and severe onset of pain, medications including narcotic analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and antispasmodics are usually recommended.[12]

Antispasmodic agents are traditionally used for relief of smooth muscle spasm in conditions such as renal colic, biliary colic, or dysmenorrhea. However, the limitations of conventional antispasmodic agents has developed the need for newer and safer antispasmodic agents for the management of various types of spasmodic pain disorders.[15,16]

Role of Drotaverine in Managing Abdominal (biliary) Colic

Drotaverine has emerged as a well-established, directly acting smooth muscle antispasmodic agent that brings about quick and effective pain relief.[17] Drotaverine inhibits phosphodiesterase type IV (PDE IV) in the smooth muscle cells that hydrolyses cyclic adenosine monophosphate (cAMP). This leads to increase in cAMP concentration, which decreases uptake of calcium (exerting mild Ca-channel blocking effect) and alters its distribution among the cells.[18,19] The two metabolites of drotaverine in the bile (a deoxy-, and a deoxy-desethyl, metabolite) are 10-times more active in inhibiting PDE IV. This property of drotaverine provides it with remarkable clinical efficacy in biliary spasm disorders. Being a highly potent and well-tolerated antispasmodic agent, drotaverine is effective for oral and parenteral administration, capable of relieving or preventing smooth muscle spasm of various other organs where PDE4 is present, including smooth muscles of the kidney or ureter.[18-20]

In fact, its effects have been confirmed for over 35 years by clinical studies on more than 10,000 patients.[18] In clinical practice, a significant advantage of drotaverine is that it is devoid of any anticholinergic side effects, unlike other available spasmolytics like dicyclomine.[17] Moreover, results from surveillance studies have shown a very advantageous feature of drotaverine, that is, the antispasmodic and analgesic effect of drotaverine does not cover or mask the leading symptoms of acute abdominal diseases. This is a distinctive effect since all other antispasmodic agents

Box 2: Benefits of drotaverine

- Effectively maintains a state of spasmolysis
- Wide therapeutic window
- Negligible drug-drug interactions
- Available as combination with aceclofenac, mefenamic acid and paracetamol
- Well-tolerated across all age groups
- Does not induce anticholinergic adverse effects such as constipation, urinary retention, dry mouth and visual disturbances, commonly seen with the use of hyoscyamine and dicyclomine
- Does not mask the symptoms of acute abdomen, and interfere with diagnosis and further treatment modalities

mask the physical "acute abdomen" making it impossible to achieve a rapid diagnosis on reaching the hospital.[20]

Drotaverine is effective in the treatment of smooth muscles spasms, which arise from nervous or muscular origin. Regardless of the type of autonomic innervation, drotaverine affects smooth muscles present in the intestines, bile ducts, urogenital system and cardiovascular system. Due to its vasodilatation effect, drotaverine improves blood flow to the tissue.[21] Box 2 illustrates various beneficial effects of drotaverine.

A placebo-controlled, multicentre, randomized, double-blind study[18] was conducted to evaluate the spasmolytic effect of drotaverine in the treatment of colicky pain. A total number of 140 patients were enrolled in the study out of which 102 completed and 38 withdrew. A visual analog scale (VAS), a four-grade pain intensity scale (PI) and a pain relief scale were used to study the changes in the intensity of pain. The primary endpoint

Figure 2: Efficacy of drotaverine in acute colicky pain

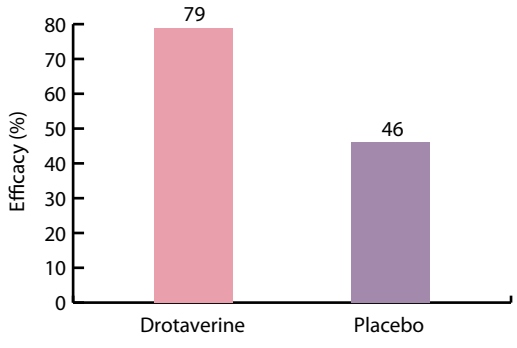
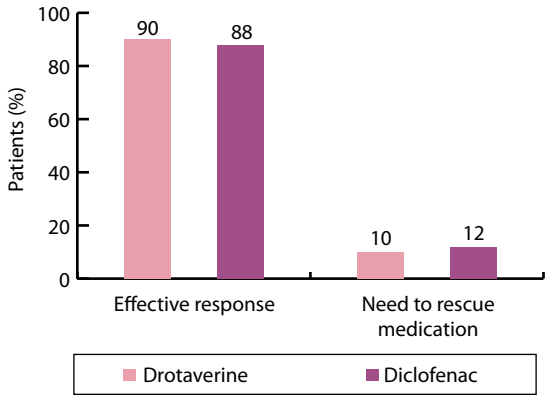


Figure 3: Comparative efficacy of drotaverine and diclofenac in colicky pain



of the study was evaluation of the antispasmodic effect of drotaverine during a 3-h study period. The painkilling effect was defined as pain reduction by at least half in the PI scale, or a ≥40% decrease in the VAS 40 min after either the first or the second injection of 80 mg drotaverine or placebo. Results divulged that drotaverine was effective in 79% of patients as compared to placebo that was effective in only 46% of the patients (Figure 2).

As well, the efficacy and safety of drotaverine as analgesic in colic episodes is noninferior to diclofenac. In a randomized, single-blind study,[22] wherein patients presenting to the emergency department with a colic episode received drotaverine (80 mg IM) or diclofenac (75 mg IM) (n=50 in both groups); after 30 minutes of drug administration, the VAS decreased significantly in both the groups. Furthermore, 90% patients in the drotaverine group and 88% in the diclofenac group found the therapy effective. The need for rescue medication was in five patients (10%) of the drotaverine group and six patients (12%) in the diclofenac group (Figure 3). Therefore, Drotaverine may be used as an effective alternative or add-on therapy in such instances to provide an augmented effect.

In routine practice, to potentiate the analgesic effect, drotaverine is usually used in combination with other analgesics like aceclofenac or mefenamic acid, which have complimentary mechanisms of action. Such combinations provide a synergistic effect, and could therefore prove highly effective in relieving acute spasmodic pain through their actions on several pain components, including those related to spasm and where several inflammatory mediators are involved.[17-19,23-25]

Aceclofenac is a long-acting, well-tolerated NSAID with fewer incidence of side effects and established safety profile, which provides sustained pain relief by preferentially blocking cyclo-oxygenase (COX) II enzyme. This profile in fact makes aceclofenac an ideal NSAID for combining with the fast acting drotaverine, for effective pain relief from post-operative procedures. Similar to the fixed dose combination (FDC) of drotaverine and aceclofenac, FDC of drotaverine and mefenamic acid has also been shown to be highly effective in relief of acute spasmodic pain.[15,17]

Conclusion

Biliary colic is the most common clinical presentation of symptomatic gallstone disease, characterized by intermittent or recurrent episodes of constant, sharp, right upper quadrant abdominal pain that may be associated with nausea and vomiting. Symptoms of biliary colic usually manifest after a large, fatty meal, since it triggers the digestive system's demand for bile leading to contraction of the gallbladder; in the event of a gallstone blocking the cystic duct or the common bile duct, the vigorous contraction of bile duct to try to move the stone causes the typical pain of biliary colic. The intensity of pain in biliary colic is generally high, thus necessitating immediate medical attention and analgesia for pain management. Antispasmodic agents are traditionally used for relief of smooth muscle spasm in conditions such as renal colic, biliary colic, or dysmenorrhoea. Drotaverine has emerged as a well established directly acting, smooth muscle antispasmodic agent that brings about quick and effective pain relief. The two metabolites of drotaverine in the bile are 10-times more active in inhibiting phosphodiesterase type IV, which provides it with remarkable clinical efficacy in biliary spasm disorders. Being a highly potent and well-tolerated antispasmodic agent, drotaverine is effective for oral and parenteral administration, capable of relieving or preventing smooth muscle spasm of various other organs where PDE IV is present. It is free of the side-effects associated with other known anticholinergic anti-spasmodics like dicyclomine. Given its efficacy in the treatment of colicky pain, it can be safely used in the treatment of biliary colic. In routine practice, to potentiate the analgesic effect, drotaverine is usually used in combination with other analgesics like aceclofenac or mefenamic acid, which have complimentary mechanisms of action. Such combinations provide a synergistic effect, and could therefore prove highly effective in relieving acute spasmodic pain through their actions on several pain components, including those related to spasm and where several inflammatory mediators are involved.

References

1. Baiu I, Hawn MT. Gallstones and Biliary Colic. *JAMA.* 2018;320(15):1612.
2. Gossman W, Dayal N, Meseeha M. Biliary Colic. [Updated 2019 Jul 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430772/. Accessed on 12/09/2019.
3. Régent D, Laurent V, Meyer-Bisch L, *et al.* [Biliary colic: imaging diagnosis]. *J Radiol.* 2006;87(4 Pt 2):413-29.
4. Duncan CB, Riall TS. Evidence-Based Current Surgical Practice: Calculous Gallbladder Disease. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract.* 2012;16(11):2011-2025.
5. Tanaja J, Meer JM. Cholelithiasis. [Updated 2019 Jan 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470440/. Accessed on 12/09/2019.
6. Reshetnyak VI. Concept of the pathogenesis and treatment of cholelithiasis. *World J Hepatol.* 2012;4(2):18–34.
7. Njeze GE. Gallstones. *Niger J Surg.* 2013;19(2):49–55.
8. Sanders G, Kingsnorth AN. Gallstones. *BMJ.* 2007;335(7614):295–299.
9. Indar AA, Beckingham IJ. Acute cholecystitis. *BMJ.* 2002;325(7365):639-643.
10. Woolf CJ. Generation of acute pain: central mechanisms. *Br Med Bull.* 1991;47(3):523-33.
11. Biliary Colic. Available at: https://www.health.harvard.edu/a_to_z/biliary-colic-a-to-z. Accessed on 12/09/2019.
12. Di Ciaula A, Wang DQ-H, Wang HH, *et al.* Targets for Current Pharmacological Therapy in Cholesterol Gallstone Disease. *Gastroenterology clinics of North America.* 2010;39(2):245-ix.
13. What is the role of MRI in the diagnosis of gallstones (cholelithiasis)? Available at https://www.medscape.com/answers/175667-10175/what-is-the-role-of-mri-in-the-diagnosis-of-gallstones-cholelithiasis. Accessed on 25/10/2019.
14. Jones MW, Ferguson T. Acalculous Cholecystitis. [Updated 2019 Apr 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459182/. Accessed on 23/10/2019.
15. Porwal A, Mahajan AD, Oswal DS, *et al.* Efficacy and Tolerability of Fixed-Dose Combination of Dexketoprofen and Dicyclomine Injection in Acute Renal Colic. *Pain Research and Treatment.* 2012;2012:295926.
16. Kulkarni KS. Antispasmodics – A New Perspective. *JAMA India.* 2001; 4(8):119-121.
17. Vinod KM, Ashish D. Oral drotaverine and aceclofenac combination versus aceclofenac alone for postoperative pain relief: a prospective randomized clinical trial. *Indian Journal of Pharmacy Practice.* 2013;6(4):18-21.
18. Romics I, Molnár DL, Timberg G, *et al.* The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int.* 2003;92(1):92-6.
19. Davenport K, Timoney AG, Keeley FX. Conventional and alternative methods for providing analgesia in renal colic. *BJU Int.* 2005;95(3):297-300.
20. Blasko G. Pharmacology, Mechanism of Action and Clinical Significance of a Convenient Antispasmodic Agent: Drotaverine. *JAMA India-The Physicians' Update.* 2001;4(12):55-6.
21. Drotaverine 40 | 80 mg film-coated tablets. Available at: file:///C:/Users/admin/Downloads/StreszczenieRmp_37119_Dospax+Forte.pdf. Accessed on 13/09/2019.
22. Dash A, Maiti R, Akantappa Bandakkanavar TK, *et al.* Intramuscular Drotaverine and Diclofenac in acute renal colic: a comparative study of analgesic efficacy and safety. *Pain Med.* 2012;13(3):466-71.
23. Pareek A, Chandurkar NB, Patil RT, *et al.* Efficacy and safety of aceclofenac and drotaverine fixed-dose combination in the treatment of primary dysmenorrhoea: a double-blind, doubledummy, randomized comparative study with aceclofenac. *Eur J Obstet Gynecol Reprod Biol.* 2010;152(1):86-90.
24. Sharma JB, Agarwal M, Karmakar D, *et al.* Evaluation of an effective and cheap analgesic protocol prior to intrauterine device insertion in a developing country. *Int J Reprod Contracept Obstet Gynecol.* 2015; 4(4):1061-1065.
25. Ortiz MI, Molina MA, Arai YC, Romanò CL. Analgesic drugs combinations in the treatment of different types of pain. *Pain Res Treat.* 2012;2012:612519.