

Research Letter: Anticholinergic Drugs and the Gallbladder —A Neglected Effect?

Gary D Friedman, MD, MS; Ninah Achacoso, MS; Laurel A Habel, PhD

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In our latest case-control screening analysis of pharmaceuticals for possible carcinogenesis,¹ with up to 50 age-, sex-, and follow-back-duration-matched controls, we noted a positive association of oxybutynin with gallbladder cancer risk. In a Kaiser Permanente Northern California database extending from 1996 through 2014, the odds ratio for 8 or more prescriptions dispensed (with at least 2 years of use) compared with 0 prescriptions dispensed was 2.65 (95% confidence interval = 1.41-4.97, $p = 0.002$), on the basis of 11 exposed cases and 238 exposed controls (unpublished data). Although this could have occurred by chance in a setting of thousands of screenings of 292 drugs and drug groups at 55 cancer sites, oxybutynin is an anticholinergic drug used to treat symptoms of an overactive urinary bladder and is known to relax smooth muscle in the gastrointestinal tract in general, with no mention of an effect on the gallbladder.² Too few patients with gallbladder cancer in the aforementioned screenings had received other drugs for overactive bladder for meaningful study.

Gallstones are an established risk factor for gallbladder cancer, but this association is not well understood, ie, whether gallstones themselves are carcinogenic, or whether gallstone formation is a marker for prolonged exposure of the gallbladder mucosa to carcinogens.³ In addition, detection bias may play a role, especially if the gallstones are symptomatic. Impaired contraction and emptying of the gallbladder is known to foster the development of gallstones.⁴ Laboratory studies have shown no evidence that oxybutynin is mutagenic or carcinogenic in rodents,² which supports the view that if oxybutynin use does predispose to gallbladder cancer, this would be

via reduced gallbladder motility associated with gallstone formation. This led us to a search of the literature aimed at physicians and the general public for information about anticholinergic drugs and gallstones. Unfortunately, we currently lack financial support for a proper study of the risk of gallstones and gallbladder cancer in relation to oxybutynin use. Such a study would require gathering detailed patient histories of oxybutynin use, gallstone disease, and gallbladder surgery, including time before membership in Kaiser Permanente, and ultrasound testing for silent gallstones, which are present in approximately 10% to 15% of adults.⁵

A PubMed search for review articles related to drugs and gallstones led to the following drugs described as promoting the formation of gallstones via impaired gallbladder motility: Postmenopausal hormones and oral contraceptives^{3-4,6-10}; somatostatin analogs, especially octreotide^{4,6,8-13}; nitric oxide donors such as glyceryl trinitrate, nitroprusside, and L-arginine; calcium channel antagonists such as nifedipine and verapamil; loperamide; calcitonin; trimebutine; ondansetron; and unspecified spasmolytics.^{8,11} Only one review article specified anticholinergic drugs as a category.¹¹ Other drugs such as ceftriaxone promote gallstone formation by changing bile composition.^{6,9,13} Two other articles dealt with immediate effects of acute administration of several different drugs¹⁴ and during parenteral nutrition, which is known to impair gallbladder contraction.¹⁵

The chapter on gallstone disease in the 10th edition of a highly respected textbook of gastroenterology, published in 2016,¹⁶ lists only 3 drugs fostering gallstone formation: Estrogens, octreotide, and ceftriaxone, with only the first 2 described

as affecting gallbladder motility.¹⁶ From the same textbook, a chapter on intestinal disorders lists the following drugs as diminishing intestinal motility: Tricyclic antidepressants, phenothiazines, some anti-Parkinson disease drugs, anticholinergics—specifically atropine, scopolamine, and belladonna alkaloids—opiates, and loperamide.¹⁷

Three online references, from WebMD,¹⁸ the National Institute of Diabetes and Digestive and Kidney Disease,¹⁹ and the Mayo Clinic,²⁰ listed hormone replacement therapy and birth control pills as drugs fostering gallstone formation. WebMD and the Mayo Clinic also mentioned some cholesterol-lowering medications without being specific. No other drugs were mentioned.

Although the association in drug screening between oxybutynin use and the risk of gallbladder cancer that triggered this brief exploration could have been a chance finding, it seems probable that insufficient attention has been paid to the effects of long-term use of anticholinergic pharmaceutical drugs on the motility of the gallbladder from the point of view of both research and clinical care. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Gary D Friedman, MD, MS, is Director Emeritus for the Division of Research in Oakland, CA. E-mail: gary.friedman@kp.org. Ninah Achacoso, MS, is a Data Consultant for the Division of Research in Oakland, CA. E-mail: ninah.s.achacoso@kp.org. Laurel A Habel, PhD, is a Senior Investigator and Section Chief for the Division of Research in Oakland, CA. E-mail: laurel.habel@kp.org.

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