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Potential Cytochrome P450 Drug-Drug Interaction Among Adult and Adolescent Patients Undergoing Tonsillectomy

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Abstract

Objective. To assess the frequency of potential drug-drug interactions affecting cytochrome P450 (CYP)–mediated metabolism of opioids among adult and adolescent patients who underwent adenotonsillectomy.

Study Design. Retrospective chart review.

Setting. Tertiary care university hospital.

Patients and Methods. A retrospective review was conducted of 279 patients who underwent adenotonsillectomy at the University of Rochester. The discharge medication list was reviewed for all patients, and their postoperative medications were compared with a reference list published by the Food and Drug Administration and the University of Indiana's Department of Clinical Pharmacology (Flockhart Table) to determine whether CYP-inducing or CYP-inhibiting medication was present.

Results. Out of 279 patients, 197 different medications were taken postoperatively. Approximately 70% of patients were taking 2 medications in addition to the standard postoperative analgesics (acetaminophen, hydrocodone, oxycodone, morphine, and/or ibuprofen). The 5 most commonly prescribed medications excluding the posttonsillectomy medications were oral contraceptives, ondansetron, amoxicillin, albuterol, and methylprednisolone. Four percent of patients were taking a medication that inhibits CYP3A4; <1% were taking a medication that induces CYP3A4; and 15% were taking a medication that inhibits CYP2D6.

Conclusions. Nearly 20% of the patients in this cohort were taking a medication that may alter opioid metabolism through induction or inhibition of CYP3A4 or CYP2D6. Some of these interactions have the potential to be more clinically relevant than others, particularly interactions that can lead to enhanced toxicity of opioids due to accumulation of active metabolites.

Keywords

adult, adenotonsillectomy, tonsillectomy, obstructive sleep apnea, medication interaction, opioid, patient safety, cytochrome P450

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Adenotonsillectomy is a commonly performed procedure that causes moderate to severe postoperative pain often requiring opioids, particularly in adult patients.[1] Achieving adequate pain control after surgery is challenging. The Food and Drug Administration (FDA) has restricted codeine and tramadol in children due to variable pharmacogenomic metabolism leading to severe respiratory complications and death.[2] In 2010, a child passed away from an inadvertent overdose of hydrocodone, and postmortem analysis found fatal concentrations of hydrocodone as well as absence of downstream metabolites such as hydromorphone. These abnormal values were later attributed to coadministration of clarithromycin (a potent cytochrome P450 3A4 [CYP3A4] inhibitor) and valproic acid.[3] More recently, the FDA released a drug safety communication highlighting these risks in children who are ultrarapid metabolizers of codeine in 2015 and applied a boxed warning label to hydrocodone for similar concerns in 2018.[4] These events spurred a strong movement to limit opioids for postoperative pain management in children, but there are fewer data clarifying optimal postoperative pain management in

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adults, who have worse posttonsillectomy pain as compared with children.[5] Furthermore, adults have risks of pharmacogenomic variability as well as pharmacodynamic interactions with other medications.

Polypharmacy must also be taken into consideration when assessing risk of drug interactions. Analysis of 2013-2014 National Health and Nutrition Examination Survey data showed that among adults aged 18 to 44 years old, 36.5% were taking at least 1 medication (32.6%, 1-4 drugs; 3.9%, ≥5 drugs). This increased to ~70% in the 45- to 64-year group.[6] Furthermore, a prospective cohort study by Doan et al detected an 80% prevalence of potential CYP450 (CYP)–mediated drug-drug interactions among 275 adults >65 years old with polypharmacy.[7]

While some physicians are aware of the risks of pharmacogenomic variability among patient populations, little attention is shown toward potential drug-drug interactions at the level of CYP450 enzymes, a pathway essential for the metabolism of commonly prescribed opioids. Specifically, codeine, hydrocodone, and oxycodone are metabolized by CYP3A4 and CYP2D6 isoforms, while morphine is metabolized mainly by glucuronidation with some potential metabolism by CYP3A4.[8] Therefore, potential drug-drug interactions affecting CYP metabolism of opioids can lead to excess opioid effects (including fatal toxicity), loss of analgesic efficacy, predisposition to other adverse effects, and misinterpretation of opioid-screening results.[8]

In 2018, Faria and colleagues determined that 3% to 5% of pediatric patients undergoing adenotonsillectomy are taking medications that potentially alter the metabolism of opioid pain medications.[9] Given that 30% of adults aged >65 years old in the United States take ≥5 drugs simultaneously, we hypothesize that there will be a greater number of medication interactions in adults than in children.[10] This study investigates the frequency with which adult patients who underwent tonsillectomy with or without adenoidectomy were discharged with opioids while taking medications known to affect CYP3A4 or CYP2D6 metabolism.

Methods

The methods used in this study were approved by the University of Rochester Institutional Review Board. Inclusion criteria included patients aged ≥16 years who had undergone tonsillectomy with or without adenoidectomy between February 2011 and March 2016 as identified by *Current Procedural Terminology* codes 42821 (adenotonsillectomy, age ≥12 years) and 42826 (tonsillectomy, age ≥12 years). Patients aged <16 years and patients who underwent these procedures as part of composite resection or other head and neck oncologic surgery were excluded. In total, 279 eligible patients were included for review.

For each patient, the discharge forms were reviewed to compile a list of prescribed postoperative medications as well as concurrent medications. These medication lists were entered into a custom Python-based computer program (version 3.6.1; Python Software Foundation), which generated a final compilation containing 197 unique medications across the sample size of this study. The medication lists generated for the 279 patients were also reviewed by a pharmacist (M.F.) to identify nonsystemically absorbed medications.

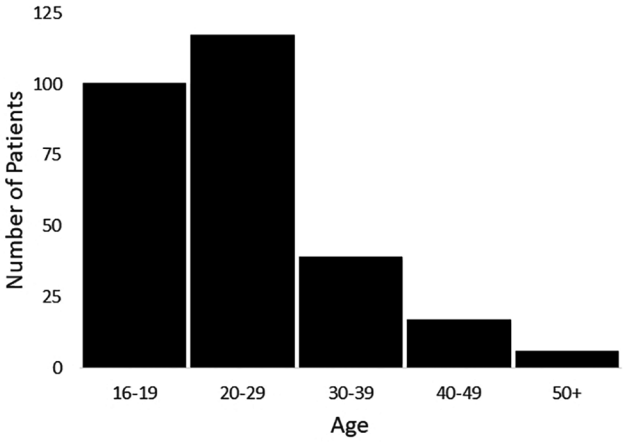

Figure 1. Number of patients in each age group.

Based on 2 published lists of medication interactions for CYP3A4 and CYP2D6 isoforms, the final medication lists were analyzed to identify potential inducers or inhibitors of these CYP enzymes. The 2 published lists chosen for comparison were the FDA table and the Flockhart Table generated by the University of Indiana School of Medicine's Department of Clinical Pharmacology.[11,12]

Results

In total, 298 adult and adolescent patients underwent tonsillectomy with or without adenoidectomy. Nineteen patients underwent tonsillectomy as part of an oncologic resection and were excluded, leaving 279 patients in this review. The average age was 25 (**Figure 1**); 32% were male. Topical medications, drops, vitamins, and other similar formulations that lacked systemic absorption were omitted from the analysis after review by a pharmacist. There were 197 medications identified with systemic absorption. The most common posttonsillectomy regimens utilized at the University of Rochester during the time of the review period included combinations of acetaminophen with oxycodone or hydrocodone and, to a lesser degree, ibuprofen. Seventy percent of patients were taking at least 2 medications in addition to the standard posttonsillectomy medications (ie, acetaminophen, hydrocodone, oxycodone, morphine, and/or ibuprofen). The mean and median numbers of discharge medications were 5.6 and 5, respectively (95% CI, 5.25-5.98). **Table 1** contains the most common medications. However, some providers did not enter over-the-counter acetaminophen or ibuprofen on patients' discharge forms; thus, their true usage is likely underrepresented in our analysis. Of note, other commonly seen discharge medications include oral contraceptive pills, antiemetics, asthma medication, and proton pump inhibitors.

Table 2 lists CYP3A4 and CYP2D6 inhibitors and inducers found within the compiled list of medications taken by our patient cohort. There were 7 CYP3A4 inhibitors, 2 types of CYP3A4 inducers, and 7 CYP2D6 inhibitors.

Table 1. Most Common Discharge Medicines.

All discharge medications	Patients, No. (%)
Posttonsillectomy medications	
Acetaminophen	247 (89)
Oxycodone	136 (49)
Hydrocodone	125 (45)
Ibuprofen	121 (43)
Non–posttonsillectomy medications	
Oral contraceptive pills	65 (23)
Ondansetron	44 (16)
Amoxicillin	42 (15)
Albuterol inhaled	31 (11)
Methylprednisolone	32 (11)
Omeprazole	31 (11)
Promethazine	27 (9)
Clindamycin	19 (7)
Clavulanate	16 (6)
Citalopram	15 (5)

Clarithromycin, fluconazole, and ketoconazole were the most commonly used CYP3A4 inhibitors, whereas fluoxetine, bupropion, and escitalopram were the most commonly used CYP2D6 inhibitors. The use of CYP3A4 inhibitors is especially notable, as these can lead to opiate toxicity. Meanwhile, the effects of CYP2D6 inhibition are inconclusive in clinical studies, which have shown contradictory effects.[8,13]

Table 3 depicts the percentage of patients who were taking medication known to alter CYP3A4 or CYP2D6 metabolism during their postoperative recovery. Of the total number of patients who were taking CYP metabolism–altering medication, most were taking some type of CYP2D6 inhibitor. Fifteen percent of patients were taking a CYP2D6-inhibiting medication according to the FDA table,[11] whereas Flockhart[12] indicates that 12% of patients were taking such medication. This discrepancy can be attributed to the FDA identifying escitalopram and desvenlafaxine as weak inhibitors of CYP2D6, but the Flockhart Table does not cite these as inhibitors.[11,12] Five patients (1.8%) had 2 CYP-interacting medications on their medication list, while no patient had >2.

Table 2. FDA[11] and Flockhart[12] Interactions With CYP3A4 and CYP2D6 Isoforms.

		Interaction strength	
Isoform: medication	Patients, No.	FDA	Flockhart
CYP3A4 inhibitor			
Clarithromycin	3	Strong	Strong
Fluconazole	2	Moderate	Moderate
Ketoconazole	2	Strong	Strong
Verapamil	2	Moderate	Moderate
Ciprofloxacin	1	Moderate	—
Ranitidine	1	Weak	—
Tacrolimus	1	Weak	—
CYP3A4 inducer			
Carbamazepine	1	Strong	—
Modafinil	1	Moderate	—
CYP2D6 inhibitor			
Fluoxetine	12	Strong	Strong
Bupropion	10	Strong	Strong
Escitalopram	7	Weak	—
Sertraline	5	Weak	Moderate
Duloxetine	4	Moderate	Moderate
Paroxetine	3	Strong	Strong
Desvenlafaxine	2	Weak	—

Abbreviations: CYP, cytochrome p450; FDA, Food and Drug Administration; OCPs, oral contraceptive pills (ethinyl estradiol, etonogestrel, levonorgestrel, medroxyprogesterone, norethindrone, norgestimate, norgestrel).

Table 3. Patients Taking Medication That Alters Opioid Metabolism by Source.

	Patients, No. (%)	
	FDA[11]	Flockhart[12]
CYP3A4 inhibitor	12 (4)	9 (3)
+ CYP2D6 inhibitor	3 (1)	
CYP2D6 inhibitor	41 (15)	33 (12)
+ CYP3A4 inducer	1 (<1)	
CYP3A4 inducer	2 (<1)	2 (<1)

Abbreviations: CYP, cytochrome p450; FDA, Food and Drug Administration.

Discussion

The purpose of this study was to determine what fraction of adult and adolescent patients who underwent tonsillectomy were also taking medications known to alter the CYP metabolism of opioids. Given that adults are significantly more likely to take multiple medications prior to surgery, we predicted that there would be a greater number of potential medication interactions in adults than in children. Several studies have examined the prevalence of polypharmacy-induced drug interactions in the pediatric population. While several studies have examined opioid interactions in the pediatric population, this is the first study to report on the frequency of potential interactions in an adolescent and adult population.[14,15]

In this study, patients were taking 197 different medications postoperatively, not including our institution's standard postoperative tonsillectomy medications (acetaminophen, hydrocodone, oxycodone, morphine, and ibuprofen). We looked for medications that acted as inducers or inhibitors of CYP2D6 or CYP3A4. CYP2D6 is responsible for the metabolism of codeine and hydrocodone, whereas oxycodone is metabolized

by both but primarily by CYP3A4.[16] With the FDA's list of CYP interactive medications, it was determined that nearly 20% of the patients in this study were taking a medication with their opioids or NSAIDs (nonsteroidal anti-inflammatory drugs) that acted as CYP3A4 inhibitors/inducers or as CYP2D6 inhibitors.

Specifically, 4% of patients in this study were taking medication that inhibited CYP3A4. This is important because CYP3A4 inhibitors, like ketoconazole, would in theory prevent the conversion of oxycodone into inactive noroxycodone.[16] This could lead to an elevated level of active oxycodone and even shunt some of its metabolism to CYP2D6, which converts oxycodone to a more active metabolite, oxymorphone. In a study where participants were randomly assigned to pretreatment with placebo, ketoconazole, and paroxetine (a CYP2D6 inhibitor) prior to oxycodone ingestion, participants who received ketoconazole had 2- to 3-fold elevated oxycodone drug concentrations as compared with those receiving placebo or paroxetine.[17,18]

Meanwhile, 15% of patients in our study were taking medication that inhibited CYP2D6, which could theoretically decrease certain opiates' conversion to more active metabolites. A study conducted by the University of Colorado showed that CYP2D6 medication users (ie, medications that inhibit or act as substrates of CYP2D6) were one-third as likely to respond to hydrocodone. There was a significant difference in hydrocodone response between those who were taking CYP2D6-altering medication and those who were not.[19] Similarly, Heiskanen and colleagues found that in patients treated with oxycodone, inhibition of CYP2D6 by quinidine led to elevated levels of noroxycodone, a less potent analgesic, while reducing the production of oxymorphone, the active metabolite.[16,18] However, other studies have not had consistent findings, with variable reports of decreased efficacy, little clinical effect, or even increased toxicity, specifically in the case of CYP2D6 poor metabolizers.[16,20]

Ultimately, alterations in opioid metabolism due to drug-drug interactions can inadvertently affect opioid concentrations, leading to subtherapeutic poor efficacy or supratherapeutic toxicity. This is especially important in the context of patients with obstructive sleep apnea, which predisposes patients for opioid-induced ventilatory impairment in the postoperative period.[21] Posttonsillectomy, adult patients with obstructive sleep apnea may be more likely to have a clinical effect from these interactions. This is further complicated by the fact that some patients are also ultrarapid metabolizers of oxycodone, which would put them at additional risk of toxic effects due to the buildup of the active metabolite, oxymorphone. Such toxic effects have been seen with ultrarapid CYP2D6 metabolizers who were treated with codeine.[17,22]

While it is unrealistic to memorize all CYP3A4 inhibitors, the most common concurrent home medications in this patient cohort were clarithromycin, fluconazole, and ketoconazole (**Table 2**). In patients taking such CYP3A4/CYP2D6-inhibiting medications, it would be safer to start with alternative analgesics, such as hydromorphone or even NSAIDs, before prescribing oxycodone.

Given the retrospective nature of this study, one of the main limitations of this study is the variability in omissions and inclusions on medication reconciliation forms among providers. For example, some providers did not document over-the-counter pain medications into the system, as evidenced by the lower-than-expected discharge rates of acetaminophen and ibuprofen: 89% and 43%, respectively. Additionally, patients may have been taking supplements or vitamins that they failed to mention, which would have been omitted from the data as well. For these reasons, the rate of potential inhibition/induction of the CYP450 system could be underestimated.

Since 35.8% (n = 100) of patients were 16 to 19 years old (**Figure 1**), it is possible that this sample was biased toward less polypharmacy than that of an older population. However, the 16- to 19-year-olds were taking an average of 4.5 medications, as compared with an average of 6.2 medications for patients aged >20 years ($P < .01$). While younger patients took fewer medications, there was still a burden of polypharmacy observed for this younger patient population.

Table 4 presents supplements not investigated in our study but found to have CYP interactions. A link to the more comprehensive list of CYP-interacting medications published by the FDA can be found in the references.[11] Another drawback in our investigation into potential drug-drug interactions is the inability to determine patients' compliance with their tonsillectomy and nontonsillectomy medications. Due to postoperative pain and possible dysphagia, patients may be less likely to adhere to their other medications during their recovery period, which our chart review would not capture. Furthermore, plasma drug concentrations would be valuable for determining whether inhibition/induction of the CYP450 system was significantly altering therapeutic levels of the prescribed opioids and may be of interest for future study.

Over the past few years, the medical field has become wary to the dangers of narcotic analgesic usage. Our study helps quantify the risk of polypharmacy and drug interactions in the adult population and further highlights the need for caution when prescribing posttonsillectomy pain medications in this patient group. Procedures such as tonsillectomy, which often require significant pain management, have been a target for reducing opioid use. While there has been some decrease in opioid prescriptions across many specialties over the past decade, a study by Choo et al found that patient-reported narcotic use is still significantly lower than the amount prescribed following tonsillectomy.[23]

Conclusion

Nearly 20% of the patients in this cohort were taking a medication that may alter opioid metabolism through induction or inhibition of CYP3A4 or CYP2D6. Some of these interactions have the potential to be more clinically relevant than others, particularly interactions that can lead to

Table 4. List of CYP2D6- and CYP3A4-Interacting Medications and Supplements.[11,24-26]

Metabolism	Medication	Supplement
CYP3A4 inhibitor		
Strong	Boceprevir, cobicistat, danoprevir, ritonavir, indinavir, elvitegravir, itraconazole, ketoconazole, lopinavir, paritaprevir, posaconazole, ombitasvir, dasabuvir, saquinavir, telaprevir, tipranavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, nelfinavir	Grapefruit juice
Moderate	Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Berberine, black cumin seed, resveratrol
Weak	Chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor	Goldenseal
Variable		Echinacea [a] and piperine [a]
CYP3A4 inducer		
Strong	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin	St John's wort
Moderate	Bosentan, efavirenz, etravirine, phenobarbital, primidone	Echinacea,[a] ginseng (Asian)
Weak	Armodafinil, modafinil, rufinamide	
CYP2D6 inhibitor		
Strong	Bupropion, fluoxetine, paroxetine, quinidine, terbinafine	Black cumin seed, resveratrol
Moderate	Abiraterone, cinacalcet, duloxetine, lorcaserin, mirabegron	Berberine
Weak	Amiodarone, celecoxib, cimetidine, clobazam, cobicistat, escitalopram, fluvoxamine, labetalol, ritonavir, sertraline, vemurafenib	Goldenseal

Abbreviation: CYP, cytochrome p450.
[a]Variable efficacy among studies.

enhanced toxicity of opioids due to accumulation of active metabolites. Due to their narrow therapeutic index, pharmacogenetic variability in the population, as well as increased risk among patients with obstructive sleep apnea, opioid concentration and interaction with other medications must be carefully considered by physicians when deciding on the type of analgesic as well as the concentration. As a result, for adult patients undergoing tonsillectomy taking concurrent CYP3A4 inhibitors, prescription of opioid analgesics that do not require metabolism via the CYP450 system should be considered, such as hydromorphone.

Author Contributions

Sai Nimmagadda, draft Institutional Review Board protocol, collect data, analyze data, draft manuscript, revise manuscript, approve manuscript, accountable for work; **Stephanie Jung-ying Wong**, analyze data, revise manuscript, approve manuscript, accountable for work; **Madlin Faria**, study conception, analyze data, revise manuscript, approve manuscript, accountable for work; **Paul Allen**, study conception, finalize Institutional Review Board protocol, analyze data, revise manuscript, approve manuscript, accountable for work; **John Faria**, study conception, finalize Institutional Review Board protocol, analyze data, revise manuscript, approve manuscript, accountable for work

Disclosures

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