Use of atropine-diphenoxylate compared with hyoscyamine to decrease rates of irinotecan-related cholinergic syndrome

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Background Cholinergic syndrome is a well established acute adverse reaction associated with irinotecan. Cholinergic side effects can be ameliorated or prevented with anticholinergic agents. To date, no formal studies have compared atropine-diphenoxylate and hyoscyamine as premedications for prophylaxis of the cholinergic syndrome with irinotecan infusion.

Objective To compare the incidence of cholinergic syndrome with irinotecan using atropine-diphenoxylate or hyoscyamine as premedication.

Methods We conducted a retrospective, single-center, nonrandomized, cohort study of adult patients treated with atropine-diphenoxylate or hyoscyamine as premedication before receiving irinotecan. For all irinotecan infusions, intravenous atropine was administered for patients experiencing any cholinergic reaction.

Results A total of 532 irinotecan cycles (354 cycles for atropine-diphenoxylate group; 178 cycles for hyoscyamine group) were analyzed in 80 patients. Overall incidence of cholinergic syndrome did not differ between atropine-diphenoxylate (8.2%) and hyoscyamine (9.0%) groups ($P = .76$). The incidence of cholinergic syndrome after the first cycle of irinotecan was similar between the 2 arms, atropine-diphenoxylate (14.6%) and hyoscyamine (10.7%), with $P = .74$. The most common cholinergic symptoms documented were abdominal pain or cramping, and diarrhea.

Limitations This study was subjected to vulnerabilities to bias and random error because of its observational retrospective design and small number of participants.

Conclusions Lack of difference in the incidence of cholinergic syndrome observed in irinotecan-treated patients suggests atropine-diphenoxylate and hyoscyamine may both be effective prophylactic options. The findings support the need for a larger, randomized study to assess and compare these agents with other potential premedications such as scopolamine and atropine in prevention of irinotecan-related cholinergic syndrome.

Irinotecan is a topoisomerase I inhibitor that creates permanent single strand DNA breaks during the replication and synthesis of DNA, leading to apoptosis of cancer cells. Irinotecan is a prodrug and its cytotoxicity is primarily attributed to the active metabolite, SN-38. Irinotecan is a widely used chemotherapeutic agent that treats a variety of malignancies, including gastrointestinal diseases such as colorectal and esophageal cancers. However, it is well established that irinotecan can cause serious adverse events, including cholinergic syndrome.[1] To date, the mechanism behind this reaction has not been clearly elucidated. There have been several explanations proposed. When irinotecan was first developed, it was discovered to be a selective and potent reversible inhibitor of human acetylcholinesterase at clinically relevant drug concentrations in a pharmacokinetic and pharmacodynamic study, which initially led researchers to believe that such properties were consistent with the acute cholinergic toxicity observed in treated patients.[2] More recently, in vivo studies with irinotecan have shown that cholinergic syndrome does not seem to be associated with the inhibition of acetylcholinesterase. Instead, the data show irinotecan activates various nerve fibers and produces vagal reflexes at peripheral sites to trigger a cholinergic response.[3] It has also been suggested that cholinergic side effects are mediated through ganglionic stimulation when irinotecan is converted to SN-38.[4]

Clinical trials have demonstrated that irinotecan-treated patients can develop acute adverse reactions such as bradycardia, decreased systolic blood pressure, hypersalivation, abdominal cramps, early diarrhea, diaphoresis, lacrimation, visual accommodation disturbances, and other manifestations of cholinergic syndrome. Typically, these symptoms occur during or shortly after intravenous irinotecan infusion and will subside or resolve within a few hours of completion of the chemotherapy.[5] Occurrence of such side effects can also be ameliorated or prevented with administration of various anticholinergics, including atropine or scopolamine.[6,7] However, standard practices or guidelines

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have yet to be established because of the variable reactions observed in patients.[8]

The package insert for irinotecan specifically states that prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.[1] Studies have shown that even though symptoms are transient, they will respond within minutes to administration of atropine at doses of 0.25-1 mg.[9] To date, there have been no prospective or retrospective studies comparing use of atropine-diphenoxylate and hyoscyamine as anticholinergic premedications for prophylaxis of cholinergic syndrome with irinotecan infusion. Therefore, we examined whether use of atropine-diphenoxylate or hyoscyamine before administration of irinotecan decreases the incidence of cholinergic syndrome.

Methods

The study protocol was approved by the institutional review boards of the Cleveland Clinic and written patient informed consent was exempt. Eligible patients for study enrollment included those who were at least 18 years old and received either atropine-diphenoxylate or hyoscyamine before administration of irinotecan. Irinotecan cycles were excluded from analysis if premedications other than atropine-diphenoxylate or hyoscyamine were given or if additional premedications were administered concomitantly with the studied prophylactic agents.

This was a retrospective, single-center, nonrandomized, cohort study that included a noninterventional retrospective medical chart review conducted for patients who were treated with irinotecan-containing order sets that included scheduled oral atropine 0.025 mg-diphenoxylate 2.5 mg or sublingual hyoscyamine 0.25 mg as premedications during October 2011-January 2014. For all irinotecan infusions regardless of which premedication was administered, atropine 0.5 mg IV was also ordered as needed for treatment of any cholinergic side effects, including shortness of breath, bradycardia, diarrhea, and abdominal cramping. Eligible patients were identified through the institution's electronic prescribing records.

The primary objective in this study was to determine the incidence of cholinergic syndrome with irinotecan in patients who received atropine-diphenoxlyate or hyoscyamine as premedication. In meeting the study's primary endpoint, cholinergic syndrome, the patients must have fulfilled 1 of 2 criteria: there must have been documented atropine use for treatment of cholinergic syndrome in the electronic prescribing records; or cholinergic symptoms must have been reported within 2 days following irinotecan administration. These reactions may have included shortness of breath, bradycardia, diarrhea, hypersalivation, abdominal pain/cramping, diaphoresis, visual impairment, flushing, rhinitis, and/or lacrimation. Secondary endpoints measured in each study group for patients who developed symptoms of cholinergic syndrome included frequency of atropine use, number of subsequent irinotecan cycles requiring additional premedications besides atropine-diphenoxylate or hyoscyamine for irinotecan infusion, number of subsequent irinotecan dose adjustments or delays owing to cholinergic side effects, and number of hospital admissions required for treatment of irinotecan-related cholinergic toxicities. For each cycle of irinotecan administered, the presence of renal impairment (defined as serum creatinine ≥ 2.0 mg/dL), hepatic dysfunction (defined as total bilirubin ≥ 1.5 mg/dL), irinotecan dose and concomitant antineoplastic agents known to have gastrointestinal side effects including diarrhea were additional data points collected from the medical record as potential risk factors for developing cholinergic syndrome.[1,2,5]

Findings from a previous study had shown that cholinergic side effects were observed during a one-time intravenous infusion of irinotecan 250 mg/m^2 in patients treated for advanced colorectal cancer. The incidence of acute cholinergic toxicities was 56% (14 of 25 patients) during irinotecan infusion.[5] On the basis of those findings, a minimal sample size of 222 cycles was calculated to detect a 20% difference in cholinergic syndrome rates between atropine-diphenoxylate and hyoscyamine groups – 56% and 36%, respectively, in all cycles to reach 80% statistical power. Groups were compared using the Fisher exact test and a 2-sided alpha of 0.05 was used to indicate statistical significance. This calculation was based on a 2:1 allocation ratio of atropine-diphenoxylate to hyoscyamine treatment arms to assess the primary outcome.

In regard to secondary outcomes, all nominal data, which included frequency of atropine use, incidence of subsequent irinotecan cycles requiring additional premedications other than atropine-diphenoxylate or hyoscyamine, incidence of irinotecan dose delay or reduction, and incidence of hospital admissions were analyzed with either the chi-square test or Fisher exact test to determine whether differences existed between the 2 study arms. All continuous data, including the mean irinotecan dose, were assessed using the Student *t* test. All tests were 2-tailed, and an alpha value less than 0.05 was predetermined to represent statistical significance. All statistical analyses were carried out using SPSS, version 11.5 (SPSS Inc, Chicago, Illinois, USA).

Results

During October 2011-January 2014, 80 adult patients who had been treated with irinotecan at the Cleveland Clinic were eligible for study enrollment. Among those patients, 532 cycles were evaluated. Atropine-diphenoxylate was administered as prophylaxis for 354 cycles (67%), whereas hyoscyamine was initiated as premedication before irinotecan infusion for 178 cycles (33%). Baseline demograph-

ics and patient characteristics were compared between the 2 study groups, and most of the patients were diagnosed with colon or rectal cancer at a median age of 59 years for the atropine-diphenoxylate group and 55 years for the hyoscyamine group (Table 1). Among all cycles, the incidence of cholinergic syndrome did not differ between the 2 groups, which was 8.2% in the atropine-diphenoxylate group and 9.0% for the hyoscyamine group (P = .76, Table 2). Similarly, the rates of cholinergic syndrome were not different between the 2 study arms after the first cycle of irinotecan, which was 14.6% for the atropine-diphenoxylate group and 10.7% for the hyoscyamine group (P = .74, Table 2).

Among 45 irinotecan cycles for which patients developed cholinergic syndrome either during or shortly after drug infusion, there were no differences with respect to presence of risk factors between the atropine-diphenoxylate and hyoscyamine groups (Table 3). Among cycles for which cholinergic syndrome was observed, the number of cycles that included concomitant antineoplastic agents (cetuximab, oxaliplatin, 5-fluorouracil, and/or bevacizumab) with irinotecan were similar between the atropine-diphenoxylate and hyoscyamine groups (86.2% and 81.3%, respectively) along with the average irinotecan dose (Table 3). In addition, atropine-diphenoxylate was administered within a median time of 60 minutes (range, 5-146 minutes) before irinotecan infusion and within 45 minutes (range, 5-240 minutes) for the hyoscyamine group. The incidence of subsequent irinotecan dose reduction and delay as well as number of cycles that required additional premedications besides atropine-diphenoxylate and hyoscyamine did not differ between the 2 groups (Table 4). Notably, a trend toward higher number of irinotecan cycles requiring additional premedications was noted in the atropine-diphenoxylate group compared with the hyoscyamine group (23.1% vs 0%, respectively; P = .15). There was also one hospital admission for bradycardia that occurred in a patient who received hyoscyamine before irinotecan infusion. However, it was noted this patient had a significant cardiac history and was being actively treated with a beta-blocker.

Discussion

Data on the prevention of irinotecan-related cholinergic syndrome are limited. There are no

TABLE 1 Baseline characteristics

Characteristic[a]	Atropine-diphenoxylate (n = 45)	Hyoscyamine (n = 28)
Median age, y (range)	59 (34-83)	55 (31-77)
Female, n (%)	17 (37.8)	13 (46.4)
Active smoker, n (%)	10 (22.2)	3 (10.7)
Median no. of cycles (range)	5 (1-27)	3 (1-12)
Cancer type, n (%)		
Adenocarcinoma of GE junction	2 (4.4)	0
Appendix	0	3 (10.7)
Breast	0	1 (3.6)
Cecum	2 (4.4)	1 (3.6)
Colon	18 (40.0)	9 (32.1)
Colorectal	1 (2.2)	1 (3.6)
Esophageal	7 (15.6)	0
Gastric	1 (2.2)	1 (3.6)
NSCLC	1 (2.2)	0
Pancreatic	4 (8.9)	5 (17.9)
Rectal	8 (17.8)	5 (17.9)
Retroperitoneal	0	1 (3.6)
SCLC	1 (2.2)	0
Unknown primary	0	1 (3.6)

GE, gastroesophageal; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer

[a]Excludes 7 patients who received atropine-diphenoxylate and hyoscyamine as premedications for different cycles throughout course of treatment.

TABLE 2 Incidence of cholinergic syndrome

	Atropine-diphenoxylate n (%)	Hyoscyamine n (%)	*P*
Incidence in all cycles[b]	29 (8.2)	16 (9.0)	0.76[a]
Incidence after first cycle[c]	7 (14.6)	3 (10.7)	0.74[d]

[a]2-sided Pearson chi-square test. [b]532 cycles analyzed (354 cycles for atropine-diphenoxylate group; 178 cycles for hyoscyamine group). [c]76 cycles analyzed (48 cycles for atropine-diphenoxylate group; 28 cycles for hyoscyamine group). [d]2-sided Fisher exact test.

TABLE 3 Presence of risk factors in 30 patients who developed cholinergic syndrome

	Atropine-diphenoxylate (29 cycles)	Hyoscyamine (16 cycles)	*P*
Scr ≥ 2.0 mg/dL, n (%)	0	0	–
Total bilirubin ≥ 1.5 mg/dL, n (%)	0	0	–
Concomitant antineoplastic agents,[a] n (%)	25 (86.2)	13 (81.3)	0.69[b]
Mean irinotecan dose, mg (SD)	149.9 (42.9)	167.5 (22.3)	0.13[c]

Scr, serum creatinine

[a]Cetuximab, oxaliplatin, 5-fluorouracil, bevacizumab. [b]2-sided Fisher exact test. [c]2-sided Student *t* test.

TABLE 4 Summary of subsequent irinotecan dose reduction, delay, and subsequent cycles requiring additional premedications

	Atropine-diphenoxylate, n (%) (26 cycles)	Hyoscyamine, n (%) (12 cycles)	P[a]
Subsequent irinotecan dose reduction	2 (7.7)	1 (8.3)	1.00
Subsequent irinotecan dose delay	1 (3.9)	1 (8.3)	0.54
Subsequent cycles requiring additional premedications	6 (23.1)	0 (0)	0.15

[a]2-sided Fisher exact test.

established guidelines available to provide specific recommendations for standardized administration of anticholinergics as premedications for irinotecan. Therefore, clinical practice seems to vary among institutions with regard to the selection of the standard agent for prophylaxis of cholinergic syndrome. Furthermore, some oncologists may be less inclined to prescribe any premedication with irinotecan infusions because of clinician preference, drug intolerance, administration issues, and/or availability of the drug.

In this retrospective study, we report the incidence of cholinergic syndrome with atropine-diphenoxylate or hyoscyamine use as premedications in 532 irinotecan cycles. In our study, no differences in the incidence of cholinergic syndrome were observed between patients who were premedicated with atropine-diphenoxylate and those premedicated with hyoscyamine among all cycles and after the first cycle of irinotecan (Table 1). Although no differences were observed between the 2 study groups, cholinergic syndrome occurred in 37.5% (30 of 80 patients), which is about half of the approximately 70% reported in irinotecan-treated patients without prophylaxis.[7,8]

On the one hand, clinical trials have reported that cholinergic reactions induced by irinotecan are generally mild to moderate in severity. On the other hand, grade 3-4 toxicities in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), including severe abdominal pain and early diarrhea, are less common and occur in about 10% of treated patients.[6,9] A nonrandomized, prospective study by Blandizzi and colleagues evaluated the cholinergic toxic syndrome in 25 patients with advanced colorectal cancer who were treated with a one-time intravenous infusion of irinotecan 250 mg/m^2 with 5-fluorouracil. Of note, these patients received a higher irinotecan dose than did the patients in our study and they did not receive any prophylactic medication for cholinergic syndrome before irinotecan administration. The adverse events were recorded in accordance with the CTCAE. In all grades (1-4), the most common acute cholinergic toxicities observed were abdominal pain, early diarrhea, and diaphoresis.[5] Similarly, our study revealed the most common cholinergic symptoms documented were abdominal pain/cramping, diarrhea, and diaphoresis in both study groups. Among patients who developed cholinergic syndrome, there was a higher percentage of diarrhea but less abdominal pain/cramping and diaphoresis reported in the hyoscyamine group (37.5%, 31.3%, 6.3%, respectively) compared with the atropine-diphenoxylate group (20.7%, 62.1%, 17.2%). However, for cycles during which cholinergic syndrome was documented, there was a higher trend of atropine use for treatment of cholinergic toxicities in the atropine-diphenoxylate group (93.1% vs 68.8%; P = .08). Of note is that additional premedications were not required for subsequent irinotecan cycles in the hyoscyamine group, compared with the 23.3% of patients in the atropine-diphenoxylate group who required additional premedications (Table 4).

These results raise the hypothesis that varying types of cholinergic side effects may respond differently to atropine-diphenoxylate and hyoscyamine, which should be considered along with patient tolerability in determining the prophylactic agent of choice before the administration of irinotecan. To date, there have been 2 published reports of prophylactic use with atropine and scopolamine to prevent irinotecan-related cholinergic syndrome.[6,7] Zampa and colleagues treated 13 patients for a total of 36 cycles with scopolamine butylbromide that was administered 30 minutes before irinotecan. None of these patients were observed to have cholinergic symptoms. However, it is important to note that the evaluated sample size was especially small.[7] Yumuk and colleagues conducted a retrospective evaluation of 66 metastatic colorectal cancer patients who were treated with 85 mg/m^2 irinotecan once a week or 350 mg/m^2 irinotecan every 3 weeks. All of the patients were administered 0.5 mg atropine sulfate subcutaneously before irinotecan infusion. Among 444 cycles, no cholinergic side effects, specifically early diarrhea were observed.[6] Although atropine seemed to be safe and effective in preventing irinotecan-induced early-onset diarrhea, recent atropine shortages as a result of manufacturing delays have been well documented by the American Society of Health-System Pharmacists and US Food and Drug Administration. In our study, atropine-diphenoxylate and hyoscyamine seemed to be generally well tolerated. The most common complaint reported by patients, especially those who received atropine-diphenoxylate, was constipation.

However, there are several limitations to this research.

Since a retrospective medical chart review was conducted, every patient who developed cholinergic syndrome may not have been captured in the electronic medical record. Another important limitation is the vulnerability to bias of an observational retrospective design. In addition, the chemotherapy regimens administered for each patient enrolled in the study comprised of varying antineoplastic agents, irinotecan dose, and total number of cycles. Furthermore, the active metabolite, SN-38, undergoes conjugation by UDP-glucuronosyl transferase 1A1 (UGT1A1) to form an inactive metabolite. Studies have demonstrated that patients homozygous for the UGT1A1*28 allele leads to increased exposure to SN-38.[10-12] We were unable to examine the impact of UGT1A1 polymorphism as a potential risk factor since the institution does not routinely provide genetic screening prior to initiation of irinotecan. There were also seven patients who received atropine-diphenoxylate and hyoscyamine as premedications for different cycles throughout the course of irinotecan treatment. Each cycle was treated independently for our statistical analysis since we assumed a minimum of 7 days that elapsed between each cycle was an adequate wash-out period based on the elimination half-lives of the parent and active compounds, 6-12 hours and 10-20 hours, respectively.[1] A study that evaluated solely the first cycle of irinotecan would have been preferred for standardization. However, because of the limited number of patients having either treatment, statistical power for the study unlikely would have been reached. Furthermore, the study's vulnerability to random error must also be acknowledged because of the small number of participants and events as the observed frequency of cholinergic events was lower than expected.

In our experience, the rates of irinotecan-related cholinergic toxicities did not differ among patients who were premedicated with atropine-diphenoxylate or hyoscyamine. Therefore, our data suggest both agents seem to be effective prophylactic options. The low cost and ease of administration associated with both medications provide additional benefits for the patient. Because of the inherent study limitations, our findings support the need of a larger, randomized study to assess and compare the efficacy and tolerability of these agents with other potential premedications such as scopolamine and atropine in the prevention of irinotecan-related cholinergic syndrome.

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