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Nicotine tartrate liquid enemas for mildly to moderately active left-sided ulcerative colitis unresponsive to first-line therapy: a pilot study

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SUMMARY

Background: Ulcerative colitis is predominantly a disease of non-smokers, and transdermal nicotine is therapeutic but often results in side-effects. Administration of nicotine as a liquid rectal enema results in less systemic nicotine absorption.

Aim: To determine the safety and clinical response of nicotine tartrate liquid enemas for active left-side ulcerative colitis in a pilot study.

Methods: Ten non-smoking patients with mildly to moderately active left-sided ulcerative colitis unresponsive to first-line therapy were treated in an open protocol with nightly nicotine tartrate liquid enemas at a dose of 3 mg nicotine base for 1 week then 6 mg for 3 weeks. Clinical assessments were determined at baseline and 4 weeks by endoscopy, physician assessment and a patient diary of daily symptoms. Peak and trough serum nicotine and trough plasma cotinine were determined by gas chromatography/mass spectrometry and high performance liquid chromatography, respectively.

Results: After 4 weeks of treatment, 5/7 patients (71%) showed clinical and sigmoidoscopic improvement (per protocol analysis). The other three patients discontinued therapy within 7 days because of inability to retain the liquid enemas. No patients showed histologic improvement. Six of the patients who completed the 4-week study had peak and trough serum nicotine concentration determined, only 1 of 6 patients had a detectable peak nicotine concentration (value 2.3 ng/mL), and all six patients had undetectable trough nicotine concentrations. The mean trough plasma cotinine concentration was 13 ± 10 ng/mL. Transient and mild adverse events occurred in 4/10 patients (nausea, lightheadedness, tremor, sleep disturbance). Given the low or undetectable serum nicotine concentrations, these adverse events are not likely to be related to the nicotine enemas.

Conclusions: Nicotine tartrate liquid enemas administrated at a dose of 3 mg nicotine base/day for 1 week and then 6 mg/day for 3 weeks are safe and appear to result in clinical improvement in some patients with mildly to moderately active, left-sided ulcerative colitis unresponsive to first-line therapy. Placebo-controlled trials are warranted to confirm these preliminary findings.

INTRODUCTION

Ulcerative colitis is primarily a disease of non-smokers.[1–3] Two-thirds of ex-smokers with ulcerative colitis

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develop the disease within 3 years after smoking cessation.[4] Non-smokers with ulcerative colitis who begin or resume smoking may go into remission.[5] These observations led to the investigation of nicotine as a therapeutic agent, beginning with uncontrolled studies of nicotine administered via gum[6,7] or a transdermal patch[8] for active ulcerative colitis. Two randomized, placebo-controlled trials of transdermal nicotine for active ulcerative colitis[9,10] both reported that the highest tolerated dose of nicotine (up to 25 mg/24 h and 22 mg/24 h, respectively) was efficacious when compared with placebo. Similarly, a controlled trial of the transdermal nicotine at the highest tolerated dose (up to 25 mg/16 h) showed equivalence to prednisolone for treatment of active ulcerative colitis. [11] In contrast, results from a controlled trial using a lower dose of transdermal nicotine (15 mg/16 h) for ulcerative colitis remission maintenance were no different than placebo.[12] Side-effects from transdermal nicotine were frequently noted in the studies discussed above and included contact dermatitis, nausea, vomiting, headaches, sleep disturbance, diaphoresis, tremor and lightheadedness.[9–12] Thus, although nicotine appears to be of benefit as a therapeutic agent for active ulcerative colitis, long-term transdermal nicotine treatment is likely to be limited by side-effects.

It is possible that nicotine administered as an enema could have a local therapeutic effect with less systemic absorption and fewer side-effects. A pharmacokinetic study in healthy volunteers demonstrated that nicotine tartrate administered as a liquid enema at a dose of 45 μg nicotine base/kg ($\approx$3 mg nicotine base for a 70 kg patient) had low systemic absorption (mean systemic bioavailability for various formulations ranged from 15–25%) and was well tolerated after a single dose.[13] Another pharmacokinetic study in both healthy volunteers and patients with active ulcerative colitis also demonstrated that 6 mg nicotine base complexed to carbomer (an acrylic acid polymer) and administered as a liquid enema had low systematic absorption and was well tolerated.[14] These studies demonstrate that administration of nicotine as an enema has the potential to reduce systemic nicotine exposure and thus decrease side-effects. However, the question of whether topical administration of nicotine can result in a local therapeutic effect in the colon of patients with ulcerative colitis has remained unanswered. We present the results of a 4-week pilot study of nicotine tartrate liquid enemas (at a dose of 3–6 mg nicotine base) administered nightly for active, left-sided ulcerative colitis.

METHODS

Patients

From April 1996 to October 1996, 10 non-smoking adult patients with active left-sided ulcerative colitis were treated nightly for 4 weeks in an open protocol with nicotine tartrate liquid enemas at doses up to 6 mg nicotine base. Eight patients were enrolled at the Mayo Clinic in Rochester, MN and two patients were enrolled at Mayo Clinic Scottsdale in Scottsdale, AZ. The study was approved by the institutional review boards of both Mayo Clinic facilities, and all patients gave written consent. Enrolment criteria included: (i) clinical, endoscopic and radiologic findings consistent with ulcerative colitis; (ii) left-sided involvement (endoscopic extent not extending proximal to the splenic flexure); and (iii) mild to moderate disease activity with a disease activity index score > 3 and ≤ 10 points on the 13-point scale discussed below. Patients were excluded if they had smoked or used nicotine-containing products in the last 3 months, or if there was evidence of renal insufficiency (serum creatinine > 1.2 mg/dL) or abnormal liver enzymes.

Concomitant medications

Patients receiving oral corticosteroids > 20 mg/day at study entry were excluded in order to avoid studying severely ill patients. Patients receiving oral corticosteroids ≤ 20 mg/day, sulphasalazine, olsalazine or oral mesalamine at a stable dose for at least 14 days were continued at that dose. Patients receiving corticosteroid or mesalamine enemas discontinued these medications 1 week prior to beginning the nicotine tartrate enemas to avoid administering more than one type of enema per day. Patients who had received other immune modifier drugs including cyclosporine, azathioprine, 6-mercaptopurine, and methotrexate within 2 months of study entry were excluded.

Nicotine tartrate liquid enema formulation

Each liquid enema was composed of: (i) 60 mL sterile water; (ii) 500 mg medium viscosity carboxymethylcellulose (Spectrum Chemical Company, Gardena, CA)

as a suspending agent; (iii) 5 g of sorbitol (Ruger, Irvington, NJ) to make the solution iso-osmolar; and (iv) a buffer system consisting of 5.23 g sodium phosphate buffer (Mallinckrodt, Paris, KY) and 0.05 g of monobasic sodium phosphate (Spectrum Chemical Company, Gardena, CA) to create a solution pH of 8.5. Nicotine in the form of nicotine tartrate (Sigma, St. Louis, MO) was added to each liquid enema as either a 3 mg nicotine base (8.552 mg nicotine tartrate) or 6 mg nicotine base (17.104 mg nicotine tartrate) dose. The resulting solution was placed in 100 mL disposable enema bottles and dispensed to the patients. This enema formulation, and its pharmacokinetic properties in healthy volunteers, have been previously described.[13] Likewise, it has been previously demonstrated that nicotine tartrate liquid enemas formulated as described above at a dose of 45 μg nicotine base/kg ($\approx$3 mg nicotine base) are stable for 4 weeks.[13]

Nicotine tartrate liquid enema treatment

Treatment consisted of one nicotine tartrate liquid enema nightly for 4 weeks. The enemas were dispensed in two doses containing 3 mg and 6 mg nicotine base. Patients were instructed to use the 3 mg liquid enemas for 1 week and then the 6 mg enemas for 3 weeks. Patients who experienced limiting adverse events (see below) while taking the 6 mg enemas on 3 consecutive days were instructed to change back to the 3 mg enemas. Patients who experienced limiting adverse events with the 3 mg enemas for 3 consecutive days were instructed to discontinue enema therapy. Patients were instructed to shake the enema bottle vigorously just before use and to retain the enema for at least 1 h and overnight if possible. The nicotine dose (3 mg or 6 mg nicotine base), the time that the enema was administered, and the duration of enema retention were recorded on a daily basis. Compliance was determined by review of the patient diaries and counting the used and unused nicotine tartrate liquid enema bottles at the week-4 visit.

Measurement of clinical disease activity

Patients recorded daily the number of their stools, any rectal bleeding, and any other symptoms coinciding with therapy that might represent adverse reactions. Patients were evaluated at study entry (using a 3-day baseline period) and after 4 weeks, according to a previously described 13-point disease activity index which measured stool frequency, rectal bleeding, sigmoidoscopic findings, and physician's global assessment.[15,16] Clinical remission was defined as a disease activity index score = 0. Clinical improvement in the absence of remission was defined as a decrease in the disease activity index greater than or equal to three points. Sigmoidoscopic remission was defined as a sigmoidoscopic findings score = 0. Sigmoidoscopic improvement in the absence of remission was defined as a decrease in the sigmoidoscopic findings score greater than or equal to one point.

Measurement of histologic disease activity

Colonic mucosal biopsies were obtained at study entry and after 4 weeks, and histologic disease activity was assessed according to a previously described five-point histologic disease activity index.[17] Assessed features included the nature (polymorphonuclear vs entirely mononuclear) and distribution (lamina propria vs cryptal) of the inflammatory cell infiltrate as well as the degree of glandular destruction and/or ulceration. Two endoscopic biopsies were obtained from the site in the rectosigmoid colon that appeared to have the most severe inflammatory change. The histologic disease activity index scores were blindly determined in random order at a single sitting by one pathologist (KPB). Histologic remission was defined as a histologic disease activity score = 0. Histologic improvement in the absence of remission was defined as a decrease in the histologic disease activity index score greater than or equal to one point.

Adverse events

Adverse events (such as lightheadedness, dizziness, nausea, vomiting or inability to retain the enema) were recorded in the patient diary. Adverse events which limited the patient's ability to take the study medication were reported to the study coordinator and the study medication therapy was changed as detailed above. Patients were specifically questioned at the week 4 visit about the following adverse events: inability to retain the liquid enema; nausea or vomiting; headaches; sleep disturbance; diaphoresis or sweating; lightheadedness or dizziness; and shakiness or tremor.

Measurement of serum nicotine and plasma continine concentrations

Serum nicotine and plasma cotinine concentrations (ng/mL) were determined at the week-4 visit with venous blood using standard assays.[18,19] The validated lower limits of detection for the serum nicotine and plasma cotinine assays were 2.0 ng/mL and 0.5 ng/mL, respectively. The T_{max} for nicotine administered as a nicotine tartrate liquid enema is 0.5–1.0 h and the half-life or $t_{1/2}$ is 1–2 h.[13] Thus, the blood samples for the peak and trough serum nicotine measurements were obtained immediately prior to (trough) and 1 h after (peak) administration of a nicotine tartrate liquid enema. Blood samples for trough plasma cotinine measurements were obtained immediately prior to administration of a nicotine tartrate liquid enema. Blood samples were processed immediately after venipuncture and serum/plasma was stored at −20 °C until assay.

Statistics

Descriptive statistics and parametric (paired *t*-test) methods were used where appropriate. In the case of missing data at the week 4 visit, the principle of the 'last value carried forward' was utilized. In all cases two-tailed tests were used with *P*-values ≤ 0.05 considered statistically significant.

RESULTS

Study enrolment

A total of 10 patients who met entry criteria were enrolled in the study. Seven patients completed the 4-week study according to protocol and three discontinued the study within 7 days because of inability to retain the enemas. The analysis includes only the results for the seven patients who actually completed the 4-week study (per protocol), but the data for the other three patients who could not retain the liquid enemas are included in the tables.

Demographic characteristics

All patients had chronically active ulcerative colitis which was resistant to first-line therapy (Table 1). The mean duration of symptoms was 241 days. Drug

Table 1. Demographic data in 10 patients with left-sided ulcerative colitis

Patient no.	Age (years)	Sex (M/F)	Former smoker	Disease extent (cm)	Disease duration (years)	Duration of flare (days)	Concurrent therapy	Failed therapy*
1	35	F	Yes	35	1.8	660	Prednisone 5 mg, SASP	CS enema† 5ASA enema‡
2	64	M	Yes	50	3.3	150	5ASA	CS enema‡
3	41	F	Yes	50	2.5	35	5ASA	5ASA enema‡
4	31	F	No	25	12.0	210	5ASA	
5	36	F	No	20	4.6	330	Prednisone 20 mg, 5ASA	Olsalazine† 5ASA enema‡ Azathioprine†
6	34	M	No	30	13.3	105	5ASA	
7	30	M	No	17	5.6	90	5ASA	5ASA enema‡
8	71	M	Yes	42	0.5	190	Prednisone 10 mg, 5ASA	SASP† CS enema‡
9	60	F	Yes	12	5.5	210		SASP† 5ASA enema‡
10	68	M	Yes	45	1.2	425	SASP	Prednisone* CS enema‡ 5ASA† 5ASA enema‡
Mean	47	5 M	6 Yes	33	5.0	241		
s.d.	17	5 F	4 No	14	4.4	187		

5ASA, oral mesalamine; 5ASA enema, mesalamine enema; CS enema, corticosteroid enema; SASP, sulphasalazine.
* Indicates other therapies failed during the current flare.
† Indicates medications discontinued > 14 days prior to study entry.
‡ Indicates medications discontinued ≤ 14 days prior to study entry.

treatments utilized during the current flare of ulcerative colitis are shown in Table 1. The mean number of medical treatments failed during the current flare was 2.9 ± 1.5 per patient, and all patients failed to respond to at least one other type of medication. Nine of 10 patients continued on at least one allowed concomitant medication during the study.

Disease activity

After 4 weeks of therapy, 4 of 7 patients had clinical improvement and one patient achieved clinical remission to give an overall clinical response of 71% (Figure 1). There was a statistically significant decrease in the mean (± s.d.) clinical disease activity index score between baseline (7.1 ± 2.0) and week 4 (3.9 ± 3.1), $P = 0.04$ (paired *t*-test) (Table 2). Even if the three patients who were not able to retain the liquid enemas are included in the results, the overall clinical response was 5 of 10 patients (50%). Similarly, after 4 weeks of therapy, 3 of 7 patients had sigmoidoscopic improvement and two patients achieved sigmoidoscopic remission to give an overall sigmoidoscopic response of 71% (Figure 1). For these seven patients, there was a statistically significant decrease in the mean sigmoidoscopic findings score between baseline (1.9 ± 0.4) and week 4 (1.0 ± 0.8), $P = 0.03$ (paired *t*-test) (Table 2). There was no evidence of histologic improvement or remission in any of the seven patients at the

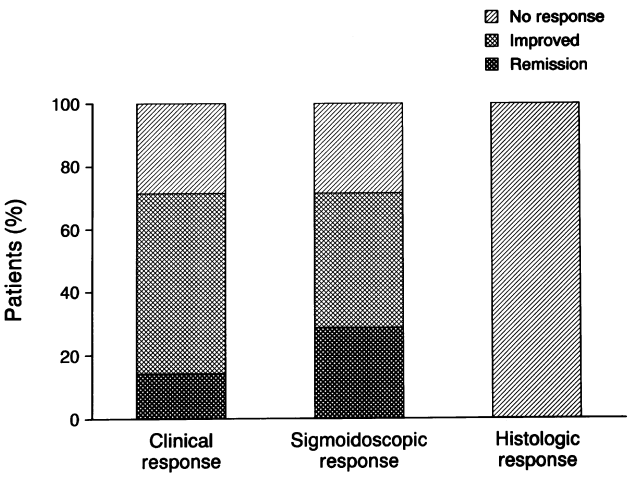

Figure 1. Percentage of seven patients who completed the 4-week study (per protocol) who had clinical, sigmoidoscopic and histologic response (improvement and/or remission) at week 4 after treatment with nicotine tartrate liquid enemas.

Table 2. Disease activity in 10 patients with left-sided ulcerative colitis

Patient no.	Clinical activity (possible values 0–13)		Sigmoidoscopic activity (possible values 0–3)		Histologic activity (possible values 0–4)	
	Baseline	Week 4	Baseline	Week 4	Baseline	Week 4
Patients who completed the 4-week study						
1	10	4	2	1	2	3
2	7	8	2	2	3	4
3	8	3	2	1	2	2
4	8	3	2	1	2	2
5	4	1	1	0	2	2
6	5	0	2	0	2	2
7	8	8	2	2	2	2
Mean ± s.d.	7.1 ± 2.0	3.9 ± 3.1*	1.9 ± 0.4	1.0 ± 0.8*	2.1 ± 0.4	2.4 ± 0.8†
Patients unable to retain the nicotine tartrate enemas						
8	9	9‡	3	3‡	3	3‡
9	6	6‡	1	1‡	3	3‡
10	7	7‡	2	2‡	3	3‡
Mean ± s.d.	7.3 ± 1.5	7.3 ± 1.5†	2.0 ± 1.0	2.0 ± 1.0†	3.0 ± 0.0	3.0 ± 0.0†
Overall						
Mean ± s.d.	7.2 ± 1.8	4.9 ± 3.1†	1.9 ± 0.6	1.3 ± 0.9†	2.4 ± 0.5	2.6 ± 0.7†

* Indicates $P \leq 0.05$ (paired *t*-test) for baseline vs. week 4.
† Indicates $P > 0.05$ (paired *t*-test) for baseline vs. week 4.
‡ Indicates last value carried forward.

end of the 4-week study (Figure 1). The mean histologic disease activity index score in the seven patients did not decrease between baseline (2.1 ± 0.4) and week 4 (2.4 ± 0.8), $P = 0.40$ (paired t-test) (Table 2). There was no difference in the duration of the ulcerative colitis flare between those patients who improved clinically or endoscopically after treatment with nicotine liquid enemas, and those patients who either did not improve or could not retain the enemas (Tables 1 and 2).

Patient compliance during the study was high; all patients administered the nicotine tartrate liquid enemas as directed on at least 90% of the days that they were in the study.

Adverse events

Adverse events occurred in 6 of 10 patients (Table 3). Three patients were unable to retain the liquid enemas because of urgency and discontinued the study within 7 days. The mean durations of enema retention for these three patients were 5, 19 and 6 min, respectively. The remaining seven patients who completed the 4-week study also had difficulty retaining the nicotine tartrate enemas for prolonged periods of time; the mean durations of enema retention for these patients were 39, 36, 48, 2, 53, 10 and 32 min. The mean ± s.d. duration of nicotine tartrate enema retention for all 10 patients was 25 ± 19 min.

None of the other adverse events (Table 3) were severe enough to result in discontinuation of nicotine tartrate liquid enema therapy before the scheduled week 4 visit. All seven of the patients who could retain the nicotine tartrate liquid enemas and complete the 4-week study were able to tolerate the 6 mg nicotine dose without limiting adverse events. The three patients who were unable to retain the nicotine tartrate liquid enemas and discontinued therapy within 7 days only received the 3 mg nicotine dose, as per protocol. Adverse events typically occurred during the first few days and then subsided.

Serum nicotine and plasma continine concentrations

The peak and trough concentrations of serum nicotine and trough concentrations of plasma cotinine at 4 weeks for the seven patients who completed the study are shown in Table 4. Only 1 of 6 patients in whom peak and trough serum nicotine concentrations were determined had a peak nicotine concentration above the 2.0 ng/mL limit of detection (value 2.3 ng/mL), and all six patients had trough nicotine concentrations below the limit of detection. Trough plasma cotinine concentrations were detectable in all seven patients, but the mean ± s.d. concentration was very low (13 ± 10 ng/mL).

DISCUSSION

Our pilot study demonstrates a clinically significant therapeutic benefit of 6 mg nicotine tartrate liquid enemas in mildly to moderately active left-sided ulcerative colitis unresponsive to first-line therapy. Three patients were unable to retain the liquid enemas and withdrew from the study within the first 7 days. The remaining seven patients continued for the full 4 weeks and the overall clinical response was 71%. Clinical improvement was demonstrated both with the 13-point clinical disease activity index and with the sigmoidoscopic findings sub-component of the index. These results are particularly striking when considering that the study patients had chronically active ulcerative colitis resistant to first-line therapy.

Table 3. Adverse events among 10 patients treated with nicotine tartrate liquid enemas*

	Patient no.										
	1	2	3	4	5	6	7	8	9	10	Total
Lightheadedness/Dizziness					X		X			X	3/10
Nausea				X	X		X				3/10
Sleep disturbance				X						X	2/10
Shakiness/Tremor					X						1/10
Inability to retain enemas								X	X	X	3/10
Any adverse reaction				X	X		X	X	X	X	6/10

* Indicates that none of the adverse events were serious or life-threatening.

Table 4. Serum nicotine and plasma cotinine concentrations in seven patients* after 4 weeks of nicotine tartrate liquid enema therapy†

Patient no.	Nicotine, ng/mL‡ Trough	Peak	Cotinine, ng/mL Trough
1	<2.0	2.3	14
2	<2.0	<2.0	6
3	<2.0	<2.0	15
4	<2.0	<2.0	5
5	<2.0	<2.0	10
6	<2.0	<2.0	3
7	NA	NA	33
Mean ± s.d.			12 ± 10

* There were 10 patients treated with nicotine enemas. However three patients, who were discontinued from nicotine enema therapy within 7 days because of inability to retain the enemas, did not have measurement of peak and trough serum nicotine and trough plasma cotinine concentrations.
† All seven patients who completed the 4-week study were able to tolerate the 6 mg dose of nicotine tartrate administered as a liquid enema.
‡ Lower limit of detection for the serum nicotine assay was 2.0 ng/mL.
NA indicates no value available due to assay failure.

The response rate to nicotine tartrate liquid enemas in our study is similar to the response rates reported in previous studies of transdermal nicotine for active ulcerative colitis, by Srivastava (67%), Pullan (49%), Sandborn (39%) and Thomas (32%).[8–11] Our results are also similar to those of Green who reported that 16/22 patients (73%) with active left-sided ulcerative colitis improved after treatment with 6 mg nicotine carbomer liquid enemas for 4 weeks in an open study.[20] Thus, based on the results of our pilot study and that of Green[20], it appears that nicotine tartrate or nicotine carbomer liquid enemas may be efficacious for the treatment of active left-sided ulcerative colitis. Placebo-controlled trials are needed to confirm these uncontrolled observations and to determine the optimal treatment duration.

All of the patients in our study who improved were receiving concomitant therapy with oral mesalamine or sulphasalazine, with or without oral corticosteroids. Similarly, most patients in previous studies of transdermal nicotine[8–11] or nicotine carbomer liquid enemas[20] for active ulcerative colitis also received concomitant therapy. Whether this observation is just coincidence or whether perhaps there is some synergy between nicotine and mesalamine or corticosteroids remains to be determined. Future studies should determine whether nicotine tartrate liquid enemas are effective as a monotherapy.

Our 4-week pilot study did not demonstrate improvement of histologic ulcerative colitis disease activity, similar to our placebo-controlled study of transdermal nicotine where histologic ulcerative colitis disease activity did not improve.[10] In contrast, a 6-week study of transdermal nicotine[8] and a 4-week study of nicotine carbomer liquid enemas[20] did demonstrate histologic improvement. Several possible explanations for this discrepancy exist. First, histologic improvement may lag behind clinical and endoscopic improvement, and the 4-week treatment duration and evaluation period in our study may not have been long enough to allow histologic improvement to occur. Second, because the colon mucosa with the most severe endoscopic inflammation was biopsied, rather than obtaining random rectosigmoid colon biopsies, there was probably a selection bias towards severe histologic inflammation, and the histologic findings in our study may not accurately reflect the overall histologic disease activity in our patients.

Only 1 of 6 patients in whom peak serum nicotine concentrations were measured had a concentration above the 2.0 ng/mL limit of detection (value 2.3 ng/mL) and all six patients in whom trough serum nicotine concentrations were measured had undetectable concentrations. The trough plasma cotinine concentrations were detectable in all seven patients but were also very low (13 ng/mL). These results are similar to those reported in a previous healthy volunteer pharmacokinetic study of hydrophilic basic nicotine tartrate liquid enemas at a dose of 45 μg nicotine base/kg ($\approx$3 mg base for a 70 kg patient) where the mean maximum serum concentration of nicotine was 2.0 ng/mL.[13] Thus, our data suggests that patients with active

ulcerative colitis treated with liquid enemas containing nicotine tartrate may experience clinical improvement from the topical (colonic) effect of nicotine, in the absence of serum nicotine concentrations that are detectable (and thus clinically important).

By comparison, in patients with ulcerative colitis treated with transdermal nicotine, the respective mean serum or plasma trough nicotine and cotinine concentrations at 6 weeks in the positive Pullan study of the 25 mg patch/24 h were 8.2 ± 7.1 ng/mL and 120 m ± 98 ng/mL;[9] and at 4 weeks in the positive Sandborn study of the 22 mg patch/24 h were 11.3 ± 8.3 ng/mL and 192 ± 95 ng/mL.[10] The negative Thomas study of the 15 mg patch/16 h reported that the respective mean week 26 trough plasma nicotine and cotinine concentrations were 5.3 ng/mL and 62 ng/mL.[12] Thus, in patients with ulcerative colitis treated with transdermal nicotine, higher serum or plasma nicotine concentrations are associated with a therapeutic effect. This is in contrast to patients treated with nicotine tartrate liquid enemas in whom the therapeutic effect is apparently unrelated to the serum nicotine concentration.

In our study, adverse events occurred in 6/10 patients: inability to retain the enema (n = 3), lightheadedness/dizziness (n = 2), nausea (n = 3), sleep disturbance (n = 1), and shakiness/tremor (n = 1). These adverse reactions were of minimal consequence, lasting at most 1–2 h and occurring on only 1–2 days in the early part of the 28-day study. Except for those patients who were not able to retain the liquid enemas, no patients required early discontinuation of the study because of adverse events. Given the very low or undetectable peak serum nicotine concentrations in this study, it seems unlikely that the observed minor adverse events were caused by the nicotine tartrate liquid enemas. These findings are in contrast to our previous study of transdermal nicotine, where adverse reactions to nicotine occurred frequently (77% of nicotine-treated patients) and they were severe enough to result in discontinuation of the nicotine in 13% of the nicotine-treated patients.[10]

Finally, the issue of formulation of nicotine liquid enemas must be addressed. In our study, 3 of 10 patients were unable to retain the liquid enemas for more than 5–19 min and discontinued the study within 7 days. These patients had previously been able to retain mesalamine or corticosteroid enemas. We have previously reported that the bioavailability of nicotine administered as either an acidic (pH = 5.5) or a basic (pH = 8.5) liquid enema is similar.[13] Thus, whether the pH is 5.5 (below the pK_1 value of 6.16) resulting in a positively-charged nicotine molecule, or the pH is 8.5 (above the pK_1 value) resulting in an uncharged nicotine base molecule, appears to make little difference in systemic nicotine absorption. We arbitrarily chose to use the basic (pH 8.5) liquid enema vehicle for this study, and it is possible that the alkalinity of our liquid enema formulation was irritating to the colonic mucosa. The nicotine itself does not seem likely to be the cause, since the nicotine carbomer enemas used by Green were easily retained by most patients.[14, 20] Future studies using nicotine enemas should consider altering the enema formulation by: (i) using foam rather than liquid enemas; (ii) using a more viscous enema vehicle; (iii) adjusting the enema pH to a more neutral or slightly acidic state; or (iv) using nicotine complexed to carbomer. A delayed-release oral formulation of nicotine tartrate or nicotine carbomer is another potential approach to improving the formulation of nicotine for delivery to the colon.[21]

In conclusion, our study demonstrates that nicotine tartrate liquid enemas administered at a dose of 3 mg nicotine base/day for 1 week and then 6 mg for 3 weeks are safe and appear to result in clinical improvement in non-smoking patients with mildly to moderately active, left-sided ulcerative colitis unresponsive to first-line therapy. Placebo-controlled trials are warranted to confirm these preliminary findings.

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