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Effects of Desipramine on Irritable Bowel Syndrome Compared with Atropine and Placebo

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Antidepressant treatment trials of irritable bowel syndrome (IBS) have suggested beneficial effects. Twenty-eight patients with the disorder (9 constipation-predominant, 19 diarrhea-predominant) completed a double-blind crossover study using desipramine, atropine, and placebo in random sequence. A four-week observation period preceded three six-week test periods. Bowel habits, abdominal distress, and affect were reported daily and in biweekly evaluations. Psychological assessments and rectosigmoid contractile studies were done in each period. Stool frequency, diarrhea, abdominal pain, depression, and slow contractions decreased significantly more in diarrhea-predominant patients during desipramine compared with placebo and atropine treatments. Diarrhea-prone patients' depression scores fell more in all periods than constipation-prone patients. Fifteen patients (13 diarrhea-predominant) improved globally during desipramine, five during placebo and six during atropine treatments. Desipramine may be helpful in treating IBS, perhaps through antidepressant and antimuscarinic effects.

Irritable bowel syndrome (IBS) may occur in 8–17% of the general population and account for 40–50% of chronic intestinal symptoms (1–4). In spite of its prevalence and frequent association with psychopathology, there have been less than 30 published reports over the past 25 years regarding psychotropic agents in the treatment of IBS and related gastrointestinal functional disorders. Many reports are difficult to interpret because of inadequate definition of IBS, lack of placebo controls, differences in assessed attributes, combining attributes, male predominance of patients (in a syndrome of high female prevalence), and use of drug combinations. In addition, noncomparable and perhaps inappropriate psychometric instruments have been used. Finally, since the predominant stooling pattern may be significant, failure to separate IBS diarrhea- and constipation-predominant subgroups may have obfuscated results.

Anxiolytic agents have been widely used in the treatment of IBS and related anxiety states, but most studies reporting management of gastrointestinal symptoms do not discriminate IBS from other functional disorders. Minor tranquilizers, with and without anticholinergics, have been reported to improve many global symptoms in some studies but not in others (5–10). Antidepressants may be more

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effective than anxiolytic agents in IBS. Three placebo-controlled trials of antidepressants alone and two with antidepressant–anxiolytic combinations have been reported (11–15). Symptoms usually improved but often no more than with placebo.

Diarrhea and abdominal pain were significantly reduced by an amitriptyline–fluphenazine combination compared with placebo (13). In a large study by Myren et al, dosing with an adequate dose of trimipramine was associated with significant reduction of IBS somatic and psychiatric symptoms (14). Symptom-related disability decreased significantly on desipramine in one study but in another trial the improvement of a cluster of IBS symptoms failed to reach the statistical significance ($P = 0.08$) (11, 12). Hislop reported that trifluoperazine did not diminish global IBS symptoms in 10 of 19 patients but seven of the nine failures subsequently treated with amitriptyline improved and five became symptom-free (16). Ritchie and Truelove found that nortriptyline–fluthemazine combination with mebeverine was more effective than lorazepam with mebeverine (15).

This study was initiated because previous data suggested that antidepressants may be helpful in IBS as well as in chronic pain (17–19). We hypothesized that desipramine would be more effective than placebo or atropine in alleviating somatic as well as associated psychiatric symptoms in IBS. A "precise" definition of IBS was considered essential, and use of a number of quantifiable variables and employment of validated, reproducible test instruments were deemed highly desirable. However, because of disagreements in the definition of IBS, uncertainty of the diagnostic role of gastrointestinal motility studies, and controversies as to appropriateness of specific psychometric tests, it was apparent that the goals could not be fully realized (20–23). Our earlier observation that a psychotropic drug should be assessed in a carefully controlled trial was an added incentive (24).

MATERIALS AND METHODS

A double-blind, crossover design was used to ascertain the effects of placebo, atropine, and desipramine on multiple somatic, psychological, and physiological attributes. For purposes of the study, IBS was defined as three or more months of abdominal pain or distress not attributed to menstruation, with diarrhea, constipation, or a variation between the two, occurring at least biweekly for which no organic cause had been found. The abdominal discomfort was usually low but often poorly localized. Diarrhea was defined as more frequent loose to liquid stools without treatment, compared to the patient's norm. The definition was not limited to more than three stools per day. Constipation was defined as less frequent and harder stools, more straining, and increased sense of incomplete emptying without intervention, compared with the patient's norm. The definition of constipation was not confined to less than three stools a week since the numerical frequency was usually of less concern to the patients than more subjective attributes (25, 26). The patients were classified as either diarrhea- or constipation-predominant based on which pattern had previously occurred most often and was most bothersome. The IBS patients were stratified into diarrhea and constipation predominance because there may be significant motility differences (27). In addition, it is our impression that the latter group are more difficult to treat.

Forty-one patients (27 women) from our Gastroenterology Clinic satisfied the criteria for IBS and entered the trial. All were white, and none had a history of lactose intolerance. Twelve patients did not complete the study, five for noncompliance, three for adverse desipramine side effects, two for scheduling conflicts, and one each for relocation and intercurrent health problems. Of the twenty-nine patients who finished the study, 18 were women. Their mean age was 45.2 years with a range from 20 to 65 years. One patient who completed the study was not included in the computations because her IBS symptoms were not classifiable into either subgroup. Nineteen had a diarrhea-predominant pattern and nine were predominantly constipated. Twenty-seven patients were assessed for Manning's criteria for IBS and 52% fulfilled three or more (28).

Patients were evaluated by comprehensive history and physical examination, which included ocular tonometry for those over 40 years, complete blood count, erythrocyte sedimentation rate, urinalysis, and multichannel biochemical profile. Stools were examined for blood, ova, and parasites and were cultured for bacterial pathogens. Proctosigmoidoscopy and barium enema were performed at screening or within the previous year. No anorectal abnormalities were found. Further evaluations were carried out if clinically indicated. The Minnesota Multiphasic Personality Inventory (MMPI) was administered at the screening visit (29, 30). Form R is a 399-item inventory to evaluate general personality traits and emotional adjustment. It has built-in validity scores and a reliability correlation of 0.76 ($P < 0.01$). Attention has been given to the "neurotic triad" as seen in the hypochondriasis, depression, and hysteria scales in IBS compared with other gastrointestinal disorders (31).

The trial included a four-week observation period and three six-week test periods, during which each patient was randomly assigned to receive one of the six possible sequences of the three test agents. To avoid carryover effects, we did not use the data collected during the first two-week "washout" periods. We urged patients to discontinue all nonessential, nonstudy medications during the trial. If this was not feasible, we requested that they record the names, doses, and time of use of these drugs. We anticipated unacceptable dropout and noncompliance rates if we insisted that all concomitant medica-

tions be stopped. The patients were not asked specifically about fiber intake.

Patients received 50-mg tablets of desipramine (Merrell Dow, Cincinnati, Ohio) with an atropine placebo (Eli Lilly, Indianapolis, Indiana), a desipramine placebo (Merrell Dow) with 0.4-mg tablets of atropine (Eli Lilly), or both placebos. One tablet of each was given daily at bedtime the first week, two the second week and three from the third through sixth weeks. Only the pharmacist member of the study team (G.E.S.) had access to the code identifying active drugs and placebos. Desipramine was selected because of its relatively low antimuscarinic effect in relation to its psychotropic activity and its minimal sedative effect (32–35). Nevertheless, since some xerostomia occurred with desipramine, atropine was used primarily to induce this symptom and incidentally to treat IBS, although the efficacy of anticholinergic treatment has been questioned (36). In this study atropine probably should be considered more as a placebo than an active agent because of its short half-life and modest dose.

During the test periods, data relating to stool frequency and consistency, frequency and intensity of abdominal distress, mood changes, and other data were recorded by the patients in a diary. The patients were also assessed biweekly by symptom questionnaires. At these visits they submitted their diaries and received new ones; test drugs were dispensed and unused drugs were returned and counted. At the end of each period patients were evaluated by two psychologists in a structured 30-min interview using the Hamilton Depression Rating Scale and the Brief Psychiatric Rating Scale (37, 38). The Brief Psychiatric Rating Scale has been used to rapidly assess mental status and the Hamilton Depression Scale to describe depressive symptoms. Interrater reliability of the participating psychologists was 0.87, 0.93 for various items, and 0.93 for total scores.

Rectosigmoid manometry was carried out by the Schuster method (27, 39). With the patients in the left lateral decubitus position two 5-cm condom balloons, 1 cm apart and connected to polyethylene tubing, were blindly inserted into the rectum so that the most cephalad balloon was approximately 14 cm from the dentate line. The balloon and tubing were passed through a steel tube over which two tandem-mounted 2- to 3-cm-long molded rubber balloons were fitted. The assembly was so positioned that the proximal and distal molded balloon impinged at the levels of the internal and external anal sphincters. When in place the rectosigmoid balloon was inflated with 10 cc of air and each anal balloon with 15 cc of air. Respirations, sensed by a thermistor at the right nostril, were simultaneously recorded. To ascertain the internal sphincter inhibitory reflex and sensation threshold, the rectosigmoid balloon was rapidly inflated with 50 cc of air which was quickly aspirated. The procedure was repeated at 5-cc decrements down to 5 cc. To determine the motility index, resistance, and frequency of slow and fast contractions, the rectosigmoid balloon was rapidly inflated with 20-cc increments of air every 2 min up to 180 cc. No standard meal or enemas were given before the procedure. Pressure changes were measured by a Beckman General Purpose Pressure Transducer and recorded on a Beckman R-611 Dynograph recorder. Records were measured and interpreted visually. The balloon manometry technique for measurement of rectosigmoid motility has been reported to show abnormalities in IBS (40, 41). The relationship of IBS symptoms to rectosigmoid motility studies has been inconsistent. Although myoelectrical activity is affected by drugs and has been claimed to show specific deviations in IBS, we chose not to measure it because of lack of relationship to symptoms in most studies (4, 21, 42–45).

Informed written consent was obtained. The study was approved by the University Committee on Research Involving Human Subjects.

The following variables were assessed:

Symptoms: (1) number of bowel movements per week; (2) number of loose stools per week; (3) pain index, rated on a 0–6 intensity scale × hours per week; (4) constipation (self-rated), rated as 0 = none, 1 = mild, 2 = moderate, 3 = moderately severe, 4 = severe per 2 weeks; (5) diarrhea (self-rated), rated as 0–4 per 2 weeks; and (6) retrospective global assessment after last test period (as no improvement or improvement, with period of occurrence).

Psychometric Testing: (1) Minnesota Multiphasic Personality Inventory at entry into the study; (2) Brief Psychiatric Rating Scale (BPRS) as 0–112; and (3) Hamilton Depression Rating Scale as 0–50.

Rectosigmoid Manometry: (1) Fast contractions as number of contractions shorter than 15 sec per 16.5 min; (2) slow contractions as number of contractions longer than 15 sec per 16.5 min; and (3) Motility index as:

$$\frac{\text{Contraction ht (mm Hg)} \times \text{duration (sec) over 16.5 min}}{2}$$

Desipramine Blood Levels: In 23 patients blood was drawn after at least five weeks of desipramine treatment to determine its serum level. Measurements were by high-pressure liquid chromatography (46, 47).

Statistical Analysis. The primary data were either frequencies or quantitative scores. The frequencies were tested by means of chi squares and the quantitative scores by means of univariate and multivariate analyses of variance and by computations of Pearson correlations. The rejection region was set at the 0.05 level. One-tailed *t* tests were applied where the directions of results were predicted. The SPSS package was used for computations.

RESULTS

Twenty-five of the 28 patients completing the trial took nonstudy medications at least once during the trials and 20 took more than one drug. Eleven patients used analgesics, nine took anxiolytics/sedatives, and seven took laxatives at some time. Bulking agents were used by five patients, antibiotics by six, antacids by two, antidiarrheals by three, and anticholinergics by three. More nonstudy drugs were used while patients were taking desipramine because of antibiotic usage during that period. Ex-

TABLE 1. INSTANCES OF CONCOMITANT MEDICATION USAGE

	PERIODS				
	Observation	*Placebo*	*Atropine*	*Despramine*	*P*
Analgesics	5	5	8	9	NS
Sedatives/ tranquilizers	6	5	7	6	NS
Laxatives	3	4	4	4	NS
Bulkers	3	5	3	2	NS
Antacids	1	1	0	1	NS
Antibiotics	0	0	1	5	<0.05
Anticho- linergics	3	1	1	1	NS
Anti-diarrheals	2	1	1	2	NS
TOTAL	23	22	25	30	NS

cept for use of the antibiotics, concomitant drugs which could effect IBS symptoms were not taken significantly more frequently during any test periods (Table 1).

Observation Period

The IBS attributes of the 28 patients who completed the study are shown during the observation period (Table 2). The only statistically significant differences were higher means for the stool frequencies, self-rated diarrhea score, and fast rectosigmoid contractions in the diarrhea-prone patients.

Test Periods

Data obtained during test periods were expressed as changes from the observation period. Interperiod statistical comparisons of the constipation-predominant subgroup were not reported because the number of patients (9) was too small for meaningful comparisons. The diarrhea-predominant patients responded more favorably to desipramine than placebo or atropine in several somatic attributes, in psychometric tests, and slow rectosigmoid contractions. This subgroup showed greater improvement in depression scores than the constipation-predominant subgroup in all test periods. Retrospectively, diarrhea-prone patients favored the desipramine period over the other test periods.

Adverse Effects

Nine patients complained of symptoms during desipramine administration; in six dose reduction alleviated adverse effects. Desipramine was stopped in three patients 3–14 days after it was

TABLE 2. ATTRIBUTES DURING OBSERVATION PERIOD

	Total IBS (N = 28) Mean + SE	*Diarrhea-predominant* (N = 19) Mean + SE	*Constipation-predominant* (N = 9) Mean +SE	*P**
Stools/week	16.65 ± 1.81	18.42 ± 2.47	12.92 ± 1.70	<0.05
Loose stools/week	5.00 ± 0.95	5.72 ± 1.04	3.65 ± 1.92	NS
Pain index	223.22 ± 35.9	196.11 ± 37.97	274.73 ± 75.5	NS
Constipation (self-rated)	1.13 ± 0.22	1.08 ± 0.25	1.22 ± 0.42	NS
Diarrhea (self-rated)	1.46 ± 0.22	1.76 ± 0.26	0.83 ± 0.34	<0.05
MMPI				
Hypochondriasis	72.96 ± 5.64	71.53 ± 2.83	76.00 ± 5.79	NS
Depression	68.64 ± 1.95	66.05 ± 4.43	70.78 ± 4.53	NS
Hysteria	68.64 ± 1.95	67.63 ± 1.92	70.78 ± 4.53	NS
Brief Psychiatric Rating Scale	45.24 ± 2.36	46.59 ± 2.55	42.38 ± 5.11	NS
Hamilton Depression Rating Scale	26.04 ± 2.05	26.00 ± 2.69	26.13 ± 3.15	NS
Slow contractions	0.37 ± 0.12	0.27 ± 0.07	0.59 ± 0.34	NS
Fast contractions	2.02 ± 0.39	2.38 ± 0.53	1.28 ± 0.35	<0.05
Motility index	3.38 ± 0.76	3.14 ± 0.66	3.87 ± 1.99	NS

*Diarrhea-predominant vs constipation-predominant.

started, and these patients were dropped from the study. The major side effects were anxiety, tremulousness, palpitations, sweating, xerostomia, and constipation. During atropine administration, seven patients had bothersome xerostomia, constipation, and palpitations but these symptoms were not severe enough to discontinue the medications. Three patients had tremulousness, xerostomia, nausea, and urticaria while taking placebo; the agent was stopped in two patients after four or more weeks on this account.

Somatic Symptoms

Number of Stools. There was a reduction in the mean number of stools per week during treatment with the three test agents but the effect was greatest during desipramine treatment and least with placebo ($P < 0.02$) (Table 3). This effect was not apparent in the constipation-predominant subgroup. Comparison of mean stool frequencies between the two subgroups was not significantly different during the test periods.

Loose Stools. The mean frequency of loose stools was not significantly reduced during the test periods (Table 3). Comparison between the diarrhea- and constipation-predominant subgroups failed to reveal significant differences within test periods.

Pain Index. The mean pain index diminished during all test periods and particularly while desipramine was taken (Table 3). (Ps for desipramine vs atropine < 0.025 and vs placebo < 0.0025). This improvement was accounted for only by the diarrhea-predominant subgroup ($P < 0.01$).

Constipation (Self-Reported). The mean constipation score increased significantly during desipramine compared with atropine period ($P < 0.05$) (Table 3). Intraperiod comparisons of subgroups revealed no significant differences.

Diarrhea (Self-Reported). The mean diarrhea score decreased during all test periods, but there were no significant differences between them (Table 3). However, a significant reduction was noted in the diarrhea-predominant subgroup during desipramine compared with placebo ($P < 0.005$). Compared with the constipation-prone, the diarrhea-predominant subgroup show a significantly lower score during desipramine dosing ($P < 0.025$).

TABLE 3. SOMATIC SYMPTOMS

	Changes from observation period			*P*		
	Placebo (P)	*Atropine (A)*	*Desipramine (D)*	*P vs A*	*P vs D*	*A vs D*
Number of stools/week						
Total group ($N = 28$)	−0.38 ± 0.97	−1.72 ± 0.80	−3.65 ± 1.51	NS	<0.025	NS
Diarrhea-pred. ($N = 19$)	0.08 ± 1.25	−1.82 ± 0.89	−4.38 ± 1.97	NS	<0.025	NS
Constip.-pred. ($N = 9$)	−1.43 ± 1.45	−1.45 ± 1.78	−2.01 ± 2.10	N too small for meaningful comparison		
Number of loose stools/week						
Total group	−0.46 ± 1.05	−1.62 ± 1.02	−2.18 ± 1.56	NS	NS	NS
Diarrhea-pred.	0.14 ± 1.14	−2.02 ± 1.18	−2.52 ± 2.04	NS	NS	NS
Constip.-pred.	−1.79 ± 2.28	−0.71 ± 2.06	−1.43 ± 2.36	N too small for meaningful comparison		
Pain index						
Total group	−13.93 ± 17.76	−20.64 ± 12.30	−58.96 ± 19.37	NS	<0.0025	<0.025
Diarrhea-pred.	−38.33 ± 18.90	−47.13 ± 14.43	−84.97 ± 24.73	NS	<0.025	NS
Constip.-pred.	40.99 ± 32.98	38.96 ± 34.83	−0.42 ± 17.56	N too small for meaningful comparison		
P (Diarrhea-pred. vs Constip.-pred.)			<0.01			
Constipation (self-reported)						
Total group	−0.20 ± 0.19	−0.30 ± 0.19	0.27 ± 0.26	NS	NS	<0.05
Diarrhea-pred.	−0.13 ± 0.25	−0.50 ± 0.25	0.18 ± 0.35	NS	NS	<0.05
Constip.-pred.	−0.33 ± 0.29	0.11 ± 0.26	0.44 ± 0.39	N too small for meaningful comparison		
Diarrhea (self-reported)						
Total group	−0.25 ± 0.20	−0.34 ± 0.17	−0.64 ± 0.26	NS	NS	NS
Diarrhea-pred.	−0.16 ± 0.27	−0.24 ± 0.19	−1.00 ± 0.31	NS	<0.005	NS
Constip.-pred.	−0.44 ± 0.26	−0.17 ± 0.33	0.11 ± 0.41	N too small for meaningful comparison		
P (Diarrhea-pred. vs Constip.-pred.)			<0.025			

TABLE 4. PSYCHIATRIC ASSESSMENT

	Changes from observation period			*P (1-tailed t test)*		
	Placebo (P)	*Atropine (A)*	*Desipramine (D)*	*P vs A*	*P vs D*	*A vs D*
Brief Psychiatric Rating Scale						
Total group (N = 28)	−0.91 ± 4.03	1.90 ± 4.81	−7.29 ± 4.06	NS	<0.05	<0.02
Diarrhea-pred. (N = 19)	−6.21 ± 5.15	−7.93 ± 4.18	−12.93 ± 5.12	NS	NS	NS
Constip.-pred. (N = 9)	9.71 ± 4.37	21.57 ± 7.96	4.00 ± 4.35	N too small for meaningful comparison		
P (1-tailed t test, Diarrhea-pred. vs Constip.-pred.)	<0.025	<0.005	<0.025			
Hamilton Depression Rating Scale						
Total group	−0.86 ± 2.81	0.76 ± 3.36	−5.19 ± 3.15	NS	NS	<.05
Diarrhea-pred.	−4.57 ± 3.34	−4.79 ± 3.36	−8.64 ± 4.06	NS	NS	NS
Constip.-pred.	6.57 ± 4.08	11.86 ± 5.79	1.71 ± 3.69	N too small for meaningful comparison		
P (1-tailed t test, Diarrhea-pred. vs Constip.-pred.)	<0.025	<0.025	<0.05			

The pain index correlated moderately well with the self-reported constipation score in the constipation-predominant subgroup and with the self-reported diarrhea score in the diarrhea-prone patients (r = 0.63 and 0.42, $P < 0.05$ and < 0.05).

Psychiatric Assessment

There was greater improvement in the mean Brief Psychiatric Rating Scale during desipramine than placebo and atropine periods (Table 4). The Hamilton Depression Rating Scale fell significantly during desipramine treatment compared with atropine period (Table 4). Although significant differences were found between desipramine and other agents in the total group, no differences were demonstrated in either subgroup. This discrepency was accounted for by the widely disparate intraperiod subgroup results. The diarrhea-predominant patients had consistently lower mean scores than the constipation-prone patients in all periods (P <0.05–<0.005).

Rectosigmoid Manometry

Slow Contractions. The mean number of slow contractions fell significantly during the desipramine period compared to placebo ($P < 0.01$) (Table 5). This effect was found only in the diarrhea-predominant subgroup. No significant differences were found between subgroups within each period.

Fast Contractions. There was no significant difference in the mean number of fast contractions be-

TABLE 5. RECTOSIGMOID MANOMETRY

	Changes from Observation Period			*P*		
	Placebo (P)	*Atropine (A)*	*Desipramine (D)*	*P vs A*	*P vs D*	*A vs D*
Slow contractions						
Total group (N = 28)	−0.02 ± 0.07	−0.08 ± 0.11	−0.16 ± 0.07	NS	<0.01	NS
Diarrhea-pred. (N = 19)	−0.01 ± 0.08	−0.05 ± 0.10	−0.15 ± 0.07	NS	<0.05	NS
Constip.-pred. (N = 9)	−0.02 ± 0.16	−0.13 ± 0.33	−0.24 ± 0.19	N too small for meaningful comparison		
Fast contractions						
Total group	−0.01 ± 0.31	−0.22 ± 0.34	−0.28 ± 0.36	NS	NS	NS
Diarrhea-pred.	−0.40 ± 0.40	−0.43 ± 0.47	−0.61 ± 0.49	NS	NS	NS
Constip.-pred.	0.77 ± 0.37	0.29 ± 0.35	0.37 ± 0.44	N too small for meaningful comparisons		
P (Diarrhea-pred. vs Constip.-pred.)	<0.025					
Motility indices						
Total group	0.37 ± 0.60	−0.78 ± 0.64	−0.81 ± 0.54	NS	NS	NS
Diarrhea-pred.	−0.35 ± 0.53	−0.65 ± 0.76	−1.32 ± 0.60	NS	NS	<0.05
Constip.-pred.	1.81 ± 1.39	−0.79 ± 1.42	0.21 ± 1.05	N too small for meaningful comparisons		

TABLE 6. BLINDED RETROSPECTIVE GLOBAL ASSESSMENT IN 28 IBS PATIENTS*

	Placebo period	*Atropine period*	*Desipramine period*
Improvement during one treatment period only	5 (3)	6 (2)	11 (10)
Improvement during placebo and desipramine periods			1 (1)
Improvement during atropine and desipramine periods			3 (2)
Totals	5 (3)	6 (2)	15 (13)

*Total number improved in period (number of diarrhea-predominant patients improved).

tween the test periods or between the subgroups (Table 5). However, the frequency of fast contractions decreased slightly during all test periods in the diarrhea-predominant patients and modestly increased in the constipation-predominant subgroup. The difference was significant only in the placebo period ($P < 0.025$).

Motility Index. The mean motility indices did not differ significantly between test periods except in the diarrhea-predominant subgroup when the desipramine was compared with atropine period ($P < 0.05$) (Table 5). Comparisons between subgroups during each test period failed to show significant differences. In the observation period the motility index correlated closely with slow contractions in the constipation-predominant patients ($r = 0.98$, $P = 0.001$) and with fast contractions in the diarrhea-predominant patients ($r = 0.89$, $P = 0.001$).

Retrospective Global Assessment

Twenty-six of 28 patients reported global improvement retrospectively during one or more trial periods. Fifteen patients improved during the desipramine period, six with atropine and five while taking the placebo. Three patients were better during both desipramine and atropine periods and one during placebo and desipramine periods (Table 6). Of the 15 patients who improved while taking desipramine, 13 (87%) were diarrhea-predominant. There was a close relationship between improvement on global assessment and pain index ($P < 0.005$) but not with other attributes.

Desipramine Blood Concentrations

Desipramine serum concentrations varied between 12 and 560 ng/ml. The levels did not correlate with any of the attributes. Neither was there correlation between the attributes and the "therapeutic window" of desipramine which has been reported to range between 40 and 160 ng/ml) (48, 49).

DISCUSSION

The greater improvement of IBS symptoms during desipramine dosing compared with atropine or placebo supports our hypothesis that tricyclic antidepressant treatment is effective in this disorder. In view of the short half-life of atropine and the bedtime dosing schedule, its effect during the daytime must have been minimal compared with desipramine with its much longer half-life. Nevertheless, patients reported xerostomia equally during atropine and desipramine dosing, and both were greater than during the placebo period ($P < 0.01$). In humans, 75–100 mg of desipramine inhibits salivary flow approximately equal to the effect of 0.05 mg of atropine (personal communication with Merrell Dow Pharmaceuticals, Inc.). Although desipramine's antimuscarinic effect is only 1/260th the potency of atropine on guinea pig ileum, on a dosage basis in this study the ratio would have narrowed to about 1:2, assuming comparable effects between the species (32–34). For these reasons we could not disprove that desipramine's effect might in part result from its antimuscarinic activity. The mechanism of action of desipramine and other tricyclic antidepressants during their period of maximum psychotropic activity is unknown. The central effects of tricyclic antidepressants on pain have been related to their antidepressant activity (18). Norepinepherine, 5-hydroxytryptamine, and possibly acetylcholine may be involved (18, 19, 50, 51). Although a β_2-adrenoceptor agonist has been reported to decrease rectosigmoid motility in humans, this effect should not be transposed to antidepressants (52). Daniel advised that ". . . great caution must be exercised in analyzing the sites and mechanism of drug action on the intestine *in vivo* . . ." because receptors with similar chemical affinities may be located on a variety of components of the gut wall (53).

The greater improvement of depression scores in

the psychometric tests in the diarrhea-predominant subgroup during all test periods compared with constipation-predominant patients may be important. No significant differences in the depression scores were found between the two subgroups in the observation period, a finding similar to that reported by Whitehead and coworkers (27). The significant reduction in stool frequency, pain index, and self-rating of diarrhea in the diarrhea-predominant group suggests that this subgroup was more responsive than constipation-prone patients to all treatments and especially to desipramine. Lancaster-Smith et al interpreted that psychiatrically normal IBS patients generally responded more readily than those who were "probably psychiatric cases" (13).

There is controversy as to whether the predominant stooling pattern is clinically significant. In this study stool frequency and perception as diarrhea appeared to separate the diarrhea-predominant from the constipation-predominant patients, whereas the frequency of loose stools and perception as constipation did not. This may be due to weakness of those attributes as discriminators, the smallness of sample size, and/or chance blurring of differences as patients varied from one stooling pattern to the other. Associations between rectosigmoid motility and stooling patterns have been emphasized and refuted (4, 54). Our observations that fast contractions occurred more than twice as often in the diarrhea-predominant as in the constipation-predominant patients concurred with Whitehead et al's observations (27). However, only slow contractions were significantly reduced in the diarrhea-predominant subgroup during the desipramine treatment period of symptomatic improvement. Nevertheless, we are reluctant to make any association between these findings at this time because of inconsistent relationships between rectosigmoid manometric data and IBS symptoms.

We were concerned that the effects of concomitant medications might significantly contaminate the results. Antibiotics were the only drugs used more often during the desipramine period. However, because these medications were more likely to cause diarrhea, this should have prejudiced against desipramine's antidiarrheal effect (Table 1). We were also concerned that the small number of constipation-predominant patients might have caused a sufficient error to obscure a favorable desipramine effect within the subgroup. We are aware that more similarity in sizes of subgroups would have made more robust comparisons.

Antidepressants may play a singular role in the management of abdominal pain and diarrhea in IBS patients, especially those with diarrhea-predominant symptoms. The mechanism of desipramine's activity is unknown but may be related to enteric and central adrenergic, muscarinic, and serotonergic activities. By simultaneously measuring contractility and myoelectric activity at various gut levels while correlating concomitant symptoms and affect, we may gain some understanding of the role of enteric neurotransmitters in gut motility in "normals" and IBS and ultimately develop more specific and effective pharmacological agents.

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