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Effects of the 5-HT_3 Antagonist, Ondansetron, on the Behavioral and Physiological Effects of Pentagastrin in Patients with Panic Disorder and Social Phobia

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Pentagastrin, a cholecystokinin (CCK) agonist, produces anxiety and panic in patients with panic disorder and social phobia. Preclinical data suggests that pentagastrin-induced anxiogenesis may be mediated via 5-HT_3 receptors. In the present study, 14 patients with panic disorder or social phobia underwent pharmacological challenge in three conditions: (1) pretreatment with saline followed by pentagastrin infusion; (2) pretreatment with ondansetron followed by pentagastrin infusion; and (3) pretreatment with saline followed by saline infusion. As expected, pentagastrin administration led to increased anxiety, physical symptoms of panic attacks, pulse, plasma adrenocorticotropic hormone (ACTH), and cortisol. Pentagastrin's behavioral effects were not blocked by ondansetron, and in fact, tended to be exaggerated. Ondansetron pretreatment did not alter the pentagastrin-induced cortisol increase but significantly prolonged the pentagastrin-induced increase in ACTH. These findings suggest that pentagastrin's behavioral effects are not mediated by 5HT_3 receptors. Mechanisms by which peripherally administered CCK agonists lead to anxiety remain to be elucidated. **[Neuropsychopharmacology 17:360–369, 1997]** *Published by Elsevier Science Inc.*

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Cholecystokinin (CCK) is one of several neuropeptides present at high concentrations in the mammalian central nervous system and gastrointestinal tract. Since the discovery and identification of CCK in the brain (Vanderhaeghen et al. 1981; Dockray 1976; Dockray et al. 1977) at concentrations higher than those of classical neurotransmitters (Crawley 1985; Moran and Schwartz 1994), there has been intense interest in the potential role of CCK in normal and abnormal neuropsychiatric states.

A substantial body of evidence points to a role for CCK in anxiety and anxiety disorders. Preclinical studies in rodents and primates have generally found CCK agonists, administered peripherally or centrally, to be anxiogenic in animal models of anxiety (for review, see van Megan et al. 1994). For example, mice, rats, and guinea pigs treated systemically with a variety of CCK agonists, including CCK-4, pentagastrin, caerulein, BOC-CCK-4, BC 197 and BDNL, show increases in anxiety when tested in the elevated plus maze, as demonstrated by decreased time spent in open arms, decreased open arm entries, or reductions in exploratory

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activity (Harro et al. 1990; Harro and Vasar 1991; Singh et al. 1991; Vasar et al. 1993, 1994; Rex et al. 1994a,b; Derrien et al. 1994). Pharmacological studies using antagonists to CCK_A and CCK_B receptor subtypes suggest that the anxiety-inducing effects of CCK are secondary to activation of CCK_B receptors (Hughes et al. 1990; Ravard and Dourish, 1990; Harro and Vasar 1991; Singh et al. 1991). In addition to blocking the anxiogenic effects of CCK agonists, CCK antagonists such as proglumide, CI-988, PD135156, davazepide, L-365,031, L-365,260, and L-364,718 have been found to be anxiolytic themselves in some animal models of anxiety (Harro et al. 1990; Hughes et al. 1990; Singh et al. 1991; Costall et al. 1991; Hendrie et al. 1993; Chopin and Briley 1993; Rex et al. 1994a; Derrien et al. 1994; Bickerdike et al. 1994).

In humans, intravenous CCK-4 and pentagastrin produce anxiety in a dose-related manner (Bradwejn et al. 1991a; McCann et al. 1995), and patients with panic disorder and social phobia are more sensitive to this effect than are healthy volunteers (Abelson and Nesse 1994; Bradwejn et al. 1991b; van Megan et al. 1994; McCann et al. 1997). As reviewed elsewhere (Bradwejn et al, 1990; Abelson and Nesse 1994; van Megan et al. 1994; McCann et al. 1997), panic attacks produced by CCK-4 and pentagastrin are described by patients as being similar to spontaneous panic attacks, though generally of shorter duration. Most (Degli Uberti et al. 1983; de Montigny 1989; Abelson et al. 1991, 1994; McCann et al. 1995, 1997) but not all (van Megen et al. 1994) studies have found that CCK-4 and pentagastrin stimulate release of ACTH and/or cortisol in humans, similar to increases seen in panic attacks provoked by intravenous sodium lactate (Liebowitz et al. 1985), yohimbine (Woods et al. 1986), caffeine (Charney et al. 1985), or carbon dioxide inhalation (Woods et al. 1988).

Despite the large body of data implicating CCK in anxiety, little is known about the mechanisms of CCK's effects or whether they are secondary to actions at peripheral or brain CCK receptors. Indeed, different laboratories have demonstrated interactions between CCK and serotonin, dopamine, GABA, and glutamate, suggesting that interactions with one or more of these neurotransmitters may be responsible for the anxiogenic effects of CCK.

Evidence suggesting that serotonin and, more specifically, 5-HT_3 receptors might be involved in CCK-induced anxiogenesis stems from a variety of sources. For example, CCK agonists are known to excite serotonin neurons in the dorsal raphe nucleus (Boden et al. 1991) and potentiate the release of cortical serotonin observed in guinea pigs tested in the elevated plus maze (Rex et al. 1994). Further, pretreatment with L-365,260, a CCK antagonist, was found to inhibit cortical serotonin release during the task (Rex et al. 1994) in addition to blocking the anxiogenic effects of BOC-CCK-4, a CCK agonist. A role for the 5-HT_3 receptor subtype in CCK's effects is suggested by studies demonstrating the ability of the 5-HT_3 receptor antagonist, ondansetron, to block the anxiogenic effects of caerulein in rats tested in the elevated plus maze (Vasar et al. 1993), and to prevent CCK release from synaptosomes derived from the cerebral cortex and nucleus accumbens septi (Paudice and Ratieri 1991). Anatomically, CCK receptors and 5-HT_3 receptors are co-localized in several peripheral and central nervous system sites potentially involved in CCK-induced anxiety, including the vagus, the area postrema, the nucleus tractus solitarius, the dorsal raphe nucleus, and the cerebral cortex. Finally, clinical data also suggest a role for the 5-HT_3 receptor in anxiety, as well as a 5-HT_3/CCK interaction. In particular, preliminary findings from two multicenter studies suggested that patients with panic disorder and social phobia benefit from chronic oral treatment with ondansetron at doses of 1–2 mg/day and 0.25 mg BID, respectively (Metz et al. 1994; Bell and De Veaugh-Geiss 1994). Unpublished data from a larger phase 3 trial of ondansetron in patients with panic disorder and social phobia indicate that only a minority of these patients benefit significantly from treatment at the doses used in these studies (Harry Bowen, Glaxo Pharmaceuticals, personal communication), although in some cases, improvement was dramatic. Ondansetron has also been reported to be effective in the treatment of bulimia, (Hartman et al. 1995) a disorder in which CCK abnormalities have been postulated (Pirke et al. 1994; Lydiard 1994). There have been no studies evaluating the anxiolytic effects of intravenous ondansetron in anxiety disorders.

The purpose of the present study was to determine whether pretreatment with ondansetron might block the anxiogenic and physiological effects of pentagastrin in patients with panic disorder and social phobia. Pentagastrin, a synthetic pentapeptide, has greater affinity but lower selectivity of the CCK_B receptor than the naturally occurring peptide, CCK-4. As with CCK-4, patients with panic disorder and social phobia have increased sensitivity to the panicogenic effects of pentagastrin (Abelson et al. 1991, 1994; van Megan et al. 1994; McCann et al. 1997). Further, when pentagastrin is administered in the context of a structured role play, the two patient groups have been shown to have similar rates of pentagastrin-induced panic attacks (McCann et al. 1997). It was hypothesized that ondansetron pretreatment would lead to significant decreases in pentagastrin-induced anxiety and panic and would also decrease the magnitude of physiological responses associated with anxiety.

METHOD

Subjects

Fourteen patients with panic disorder ($n = 8$) or generalized social phobia ($n = 6$) and a mean age of 41.7 ($\pm$ 7.9) were recruited to participate in this study. All

patients were actively symptomatic and moderately to severely impaired by their anxiety disorder. Eight subjects were men, and six were women. Subjects were in good general health as determined by medical history, physical exam, electrocardiogram, and blood and urine chemistries, including a complete blood count, liver and thyroid function tests, hepatitis and HIV screens, routine urinalyses and urine drug screens for therapeutic and illicit drugs. Presence (or absence) of DSM-III-R Axis I psychiatric diagnoses was determined using a structured psychiatric interview (SADS-LA(R); Schleyer et al. 1990). Subjects were recruited through advertisements in local and college newspapers. Written informed consent was given by all study participants, who agreed to refrain from ingestion of caffeine, alcohol, and all medications for 2 weeks before study participation. Subjects who had previously been taking fluoxetine discontinued medications at least 3 weeks before the first challenge. In addition, subjects were instructed to maintain a low monoamine diet for 3 days before the study and fasted after midnight on the morning of each study day.

Design

Subjects came to an outpatient psychiatry clinic for three separate challenge sessions separated by at least 2 days. Two days between challenges was felt to be sufficient for drug washout since the half-lives of pentagastrin and ondansetron are less than 1 hour (Crawley 1988) and 3.5 h (Roila and Del Favero 1995), respectively. Challenges were performed in random order in double-blind fashion, with three possible drug combinations: (1) ondansetron pretreatment followed by pentagastrin infusion; (2) placebo pretreatment followed by pentagastrin infusion; and (3) placebo pretreatment followed by placebo infusion.

On each of the 3 challenge days, at approximately 9:30 A.M. (the −105 minute time point, or 105 minutes before the pentagastrin infusion paradigm) an intravenous (IV) catheter was placed in the left antecubital vein. On the right arm, an automated blood pressure cuff (Dinamapp, Critikon, Tampa, FL) was placed to monitor blood pressure and pulse. Subjects remained seated in a partially reclined chair (70°) for the entire procedure. Immediately after IV insertion, a curtain was drawn between the patient and the research nurse so that patients were unaware of the timing of infusions. Forty-five minutes after IV insertion (−60 min), a baseline blood sample was drawn and patients completed a baseline rating packet that included a clinician-rated Zung anxiety scale (Zung 1971), visual analog scales (VAS) for anxiety and panicky feelings, the Spielberger state anxiety scale (Spielberger et al. 1970), a DSM-IV panic symptom checklist, and a symptom checklist for the evaluation of nonspecific side effects. A second blood sample was drawn at −45 min. At −30 min, ondansetron (0.15 mg/kg, in a volume of 50 cc 0.9% NaCl) or placebo (0.9% NaCl) was infused over 15 min. This dose of ondansetron was chosen because it has been shown to be highly effective as an antiemetic (Hesketh et al. 1989). Fifteen minutes before the pentagastrin infusion paradigm (−15 min), a third blood sample (baseline #2) was collected and the baseline behavioral ratings were repeated. At time 0 (0 min) the patient began a 5-min structured social interaction task (see below) and a fourth blood sample was collected. One minute and 45 seconds into the social interaction task (1 min 45 s), pentagastrin, at a dose of 0.6 μg/kg (or normal saline at an equal volume of 20 cc), was administered over 60 s. This dose has been shown to be effective for inducing panic attacks in patients with panic disorder and social phobia (Abelson and Nesse 1994; van Megan et al. 1994; McCann et al. 1997). The timing of the ondansetron pretreatment and pentagastrin infusions was selected because plasma levels of ondansetron are known to peak approximately 30 min after infusion. After completion of the pentagastrin infusion, the intravenous line was flushed with 10 cc of normal saline (+2 min 45 s until +3 min), and four additional blood samples were obtained in succession (approximately +3 min to +6 min).

Immediately after the completion of the role play (+5 min), the patients were asked to complete visual analog scales for anxiety and self consciousness, retrospectively rating sensations that they experienced during the most intense portion of the social interaction task (the "peak" time point) and another set of visual analog scales referring to their sensations at that moment (the "post" time point). They then completed a larger packet of retrospective questionnaires (the same packet as that completed at baseline) corresponding to their peak experiences during the role play. It typically took a subject five minutes to complete all of the peak and post social interaction task ratings. Subsequent blood samples and visual analog scales for anxiety, self-consciousness, and panicky feelings were collected 30 min, 60 min, and 90 min after the initiation of the social interaction task. The baseline rating packet was completed again at the +90-min item point, after which the IV was removed.

Structured Social Interaction Task

As indicated above, subjects received pentagastrin while participating in a structured role play, as previously described (McCann et al. 1995, 1997). In addition to providing a consistent setting for infusions (presumably decreasing variability that is inherent in nonstructured infusion procedures), it is contextually appropriate for patients with social phobia. During the role play subjects were instructed to imagine that they were at a dinner party, and that they would be seated next to a stranger of the opposite sex (the confederate), who en-

tered the room immediately before the social interaction task. The stranger was described as reserved, and thus it would be the subject's responsibility to initiate and maintain a 5-min conversation. The entire role play was videotaped, with the video camera in full view of the subject. Separate confederates were used for the three different challenge days. The confederate was blind to the patient's diagnosis.

Physiological Measures

Blood samples were immediately placed on ice and were subsequently centrifuged for 10 min at 3600 rpm for plasma separation. Plasma samples were stored in a −70°C freezer for subsequent plasma cortisol, adrenocorticotropic hormone (ACTH), and growth hormone assay. Measures of blood pressure and pulse were taken at the time of each blood draw and every 2 min during the role play.

Statistical Analyses

Data were analyzed by repeated measures ANOVA with Greenhouse-Geisser corrections. For behavioral data, time points used in the analysis were −60 min (baseline #1), −15 min (+15 min after pretreatment with ondansetron/placebo), 5 min (retrospective peak ratings), and 90 (recovery). For cardiovascular measures, six time points were used: pre-ondansetron (the mean of −60 and −45 minute values), pre-pentagastrin (−15), +30, +60, and +90 minutes. For ACTH, cortisol and growth hormone analyses, seven time points were used: pre-ondansetron (the mean of −60 and −45 minute samples), pre-pentagastrin (−15), +1 (1 min into the role play, before pentagastrin infusion), +3–6 minutes (the mean of the two highest values from the six blood samples taken in succession after pentagastrin infusion), +30, +60, and +90 minutes. Results were considered significant at a level of $p < .05$. When significant main effects of drug or time, or significant drug × time interactions were observed, Bonferroni post hoc tests (Woolson 1987) were performed at peak time points to determine which drug conditions differed significantly. For comparisons involving the panic attack symptom scale (total score and individual symptoms), repeated measures ANOVA were performed at the peak time point only (since this measure was only collected once). When a significant main effect of drug was observed, Bonferroni post hoc tests were performed to determine which drug conditions differed significantly. Analysis of pentagastrin-induced side effects was conducted by totaling all side effect ratings from the symptom checklist, and averaging the ratings for each drug condition. All statistical analyses were carried out using SPSS for Windows (SPSS, Chicago, IL).

Panic attacks were defined as at least four of 12 symptoms listed in DSM-IV criteria for panic, in moderate to severe intensity (the symptom of stomach discomfort was not included, since it was an expected pentagastrin side effect). Further, only one of the symptoms reported could be "fear of dying" or "fear of going crazy" (i.e., if a patient reported both of these symptoms, it was counted only once, and three other symptoms were also required).

RESULTS

Subject Population

Diagnoses. In addition to their primary diagnosis of panic disorder or social phobia, the majority of subjects had at least one concurrent diagnosis, the most frequent being major depressive disorder (35.7%), 35.7% of subjects had a past history of dysthymia and, 35.7% met criteria for past substance abuse or dependence.

Demographics. Fifty percent of subjects were married, 35.7% were single, and 14.3% divorced, 21.4% of subjects had received an advanced degree, 35.7% had completed college but not graduate school, and 42.9% had not received further degrees after graduating from high school.

Behavioral Ratings

Zung Anxiety Status Inventory (Figure 1A). Main effects of drug [$F(2,22) = 7.6$, $p = .005$] and time [$F(3,33) = 20.1$, $p < .001$] were observed on Zung Anxiety Status Inventory scores, as well as an interaction between drug and time [$F(6,66) = 5.8$, $p = .006$]. These results reflect increased anxiety after pentagastrin infusions, with peak anxiety occurring during the role-play/pentagastrin infusion period.

Post hoc comparisons reveal that peak anxiety was significantly greater after pentagastrin than after placebo. Ondansetron pretreatment tended to enhance, rather than block, pentagastrin-induced anxiety, although this difference was not statistically significant (uncorrected $p = .2$).

Spielberger State Anxiety. A main effect of time [$F(3, 39) = 19.0$, $p < .001$] but no significant drug effect or drug × time interaction was seen on this scale, reflecting the anxiogenic effect of the experimental procedure alone.

Visual Analog Scales (Figures 1B and C). A main effect of time and a significant drug × time interaction were observed on the VAS for Anxiety [$F(6,78) = 19.0$, $p < .001$ and $F(12,156) = 3.8$, $p = .004$, respectively], on the VAS for Self-Consciousness [$F(6,78) = 14.4$, $p < .001$ and $F(12,156) = 2.6$, $p = .04$, respectively] and on the VAS for Panicky Feelings [$F(6,72) = 17.7$, $p < .001$ and $F(12,144) = 4.0$, $p = .007$, respectively].

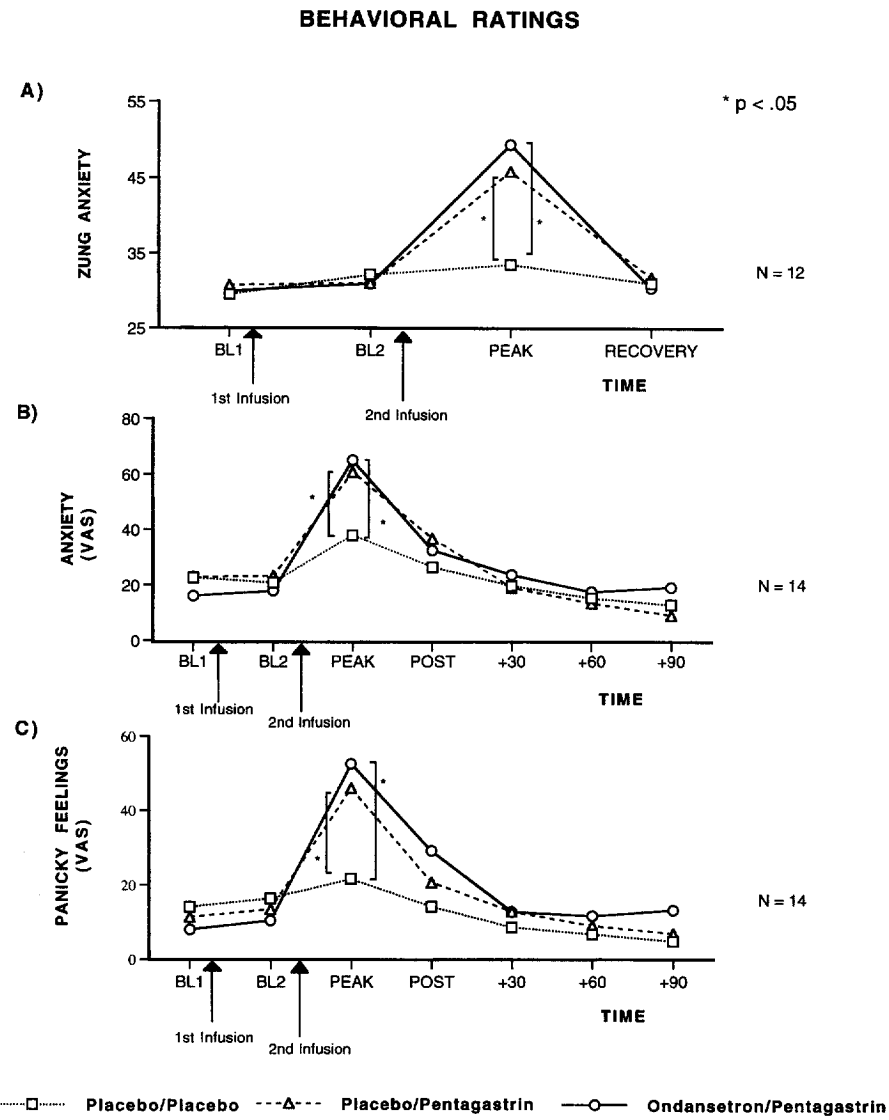

Figure 1. Effects of ondansetron pretreatment on pentagastrin-induced changes in anxiety in patients with panic disorder and social phobia. Peak measurements are group means of the most intense symptoms experienced during the social interaction task/infusion procedure. Post measurements are group means of symptom severity immediately after concluding the social interaction task. Asterisks indicate significant differences at a level of $p < .05$ as measured by Bonferroni post hoc tests.

Time effects suggest that the infusion procedure itself had an anxiogenic effect, but post hoc comparisons demonstrate that pentagastrin significantly increased anxiety, self-consciousness, and panicky feelings compared to levels of these measures seen after placebo. Ondansetron pretreatment consistently seemed to aggravate, rather than attenuate, pentagastrin effects, although this difference was not significant (uncorrected p values for anxiety, self-consciousness and panicky feelings analogs = .45, .45, and .15, respectively).

Panic Attack Symptom Scale. Significant main effects of drug were seen on the total score of the panic attack symptom scale [$F(2,26) = 13.4$, $p < .001$], reflecting differences in the presence and intensity of panic attack symptoms following either active drug combination. Post hoc comparisons revealed that peak panic attack symptoms in the placebo/pentagastrin condition and the ondansetron/pentagastrin condition were greater than those in the placebo/placebo condition, but that the two active drug combinations produced similar levels of panic symptoms. When ANOVAs were performed for individual panic attack symptoms, main effects of drug were found for palpitations [$F(2,26) = 5.9$, $p = .02$], shortness of breath [$F(2,26) = 6.7$, $p = .005$]; choking [$F(2,26) = 4.8$, $p = .03$], nausea [$(2,26) = 5.6$, $p = .018$], chills or hot flashed [$F(2,26) = 5.2$, $p = .02$], dizziness or lightheadedness [$F(2,26) = 4.6$, $p = .02$], and fear of going crazy [$F(2,26) = 5.0$, $p = .03$]. Post hoc tests revealed significant differences between both active drug conditions and the placebo/placebo condition for all of these symptoms except "fear of going crazy," where only the placebo/pentagastrin condition differed significantly from the placebo/placebo condition. No significant differences were found between the placebo/pentagastrin and ondansetron/pentagastrin conditions for any individual panic attack symptom. Five of 14 patients (36%) had panic attacks in the placebo/pentagas-

trin condition symptom. Five of 14 patients (36%) had panic attacks in the placebo/pentagastrin condition [three with panic disorder (38%) and two with social phobia (33%)], six of 14 patients (43%) had panic attacks in the ondansetron/pentagastrin condition [four with panic disorder (50%) and two with social phobia (33%)] and no patient had a panic attack in the placebo/placebo condition.

Symptom Checklist (Figure 2). Main effects of drug [$F(2,24) = 9.6$, $p = .001$], time [$F(3,36) = 7.6$, $p = .002$] and an interaction between drug and time [$F(6,72) = 7.6$, $p = .001$] were observed on the physical symptom checklist, reflecting an increase in nonspecific physical symptoms after the pentagastrin infusion.

Post hoc comparisons show that subjects reported significantly more side effects after receiving either of the two active drug combinations (placebo/pentagastrin or ondansetron/pentagastrin) when compared to the placebo/placebo combination. Ondansetron pretreatment significantly increased the number of symptoms reported after pentagastrin infusion.

Physiological Measures (Figure 3)

Cardiovascular

1. MEAN ARTERIAL BLOOD PRESSURE (MAP). A main effect of time on MAP was observed [$F(5,65) = 38.03$, $p < .001$], with no main effect of drug or interaction between drug and time, reflecting an increased MAP during the role play/pentagastrin procedure.

2. PULSE (FIGURE 3A). Pulse rates also peaked during the role play, as reflected by a main effect of time [$F(5,65) = 42.97$, $p < .001$] and an interaction between drug and time [$F(10,130) = 4.39$, $p = .015$]. Post hoc comparisons show that the placebo/pentagastrin condition was associated with greater pulse rates than the placebo/placebo condition, and that rather than attenuating this effect, ondansetron pretreatment led to significantly greater increases in pulse following pentagastrin.

Neuroendocrine

1. ACTH (FIGURE 3B). Main effects of drug and time [$F(2,24) = 3.8$, $p = .04$ and $F(6,72) = 9.0$, $p = .003$,

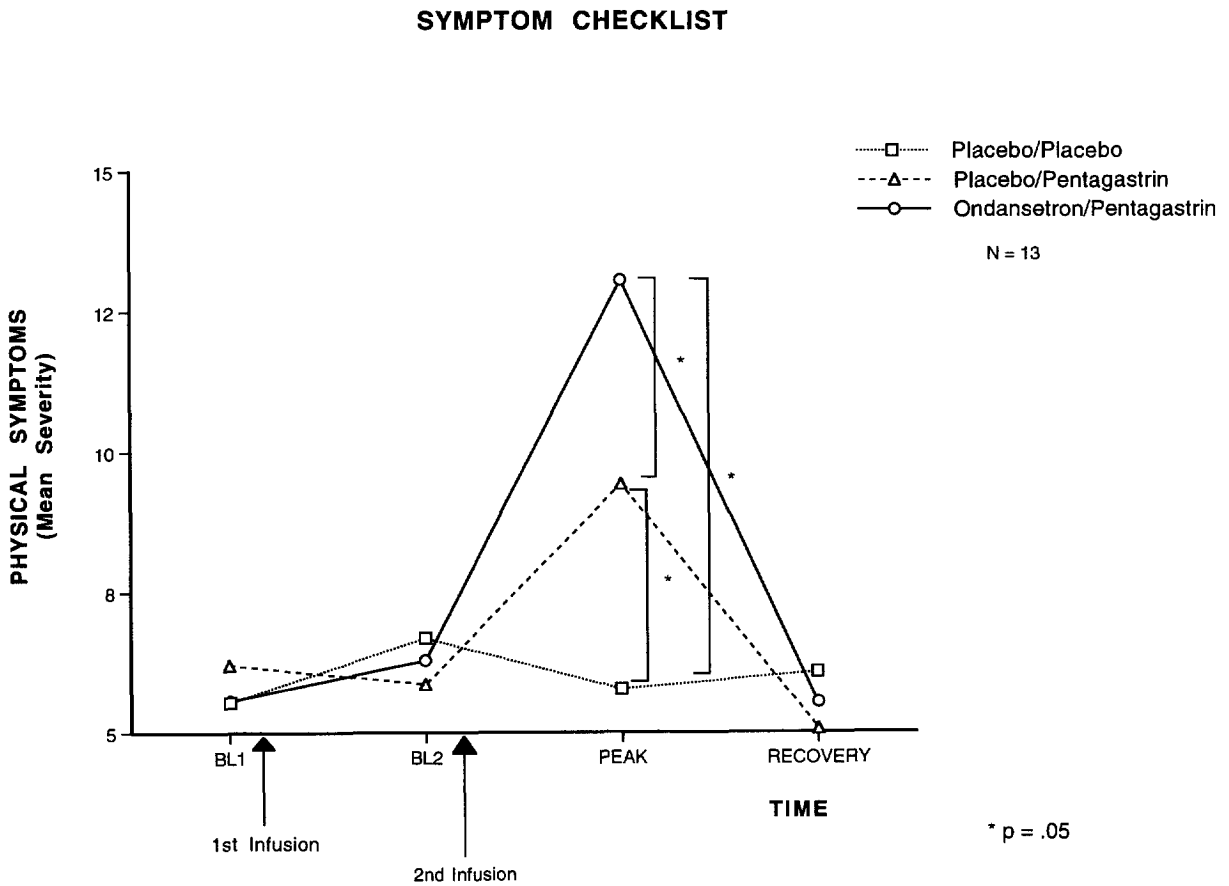

Figure 2. Effects of ondansetron on pentagastrin-induced side effects in patients with panic disorder and social phobia. Peak measurements are group means of the most intense symptoms experienced during the social interaction task/infusion procedure. Post measurements are group means of symptom severity immediately after concluding the social interaction task. Asterisks indicate significant differences at a level of $p < .05$ as measured by Bonferroni post hoc tests.

respectively] and an interaction between drug and time [F(12,144) = 3.6, p = .04] were observed for ACTH levels, reflecting increases in plasma concentrations of ACTH with peak levels occurring during the role play/pentagastrin infusion procedure.

Post hoc tests were performed at both peak and +30-min time points because of apparent lingering effects seen in the ondansetron/pentagastrin condition. These analyses revealed that, as expected, pentagastrin infusion led to significant increases in plasma ACTH, and that ACTH concentrations returned to baseline by the +30-time point. Ondansetron pretreatment tended to blunt peak pentagastrin-induced ACTH responses, and prolonged the pentagastrin-induced ACTH response, so that ACTH levels continued to be significantly greater in the ondansetron/pentagastrin condition at +30-min when compared with those seen in the placebo/placebo condition. There were no significant differences between ACTH levels from the placebo/pentagastrin and ondansetron/pentagastrin conditions at any time point.

2. CORTISOL (FIGURE 3C). A main effect of time [F(6,72) = 6.94, p = .001] but no drug effect or interaction between drug and time were observed on measures of cortisol. All three conditions led to similar increases in cortisol levels during the role play, which once again indicates the impact of the infusion paradigm itself. Although there was a trend for pentagastrin to further increase cortisol levels at the +30 time point, this difference did not reach significance.

3. GROWTH HORMONE. No main effect of drug or time, or interaction between drug and time were found for growth hormone measures.

Tabulated raw data for all measures are available upon request.

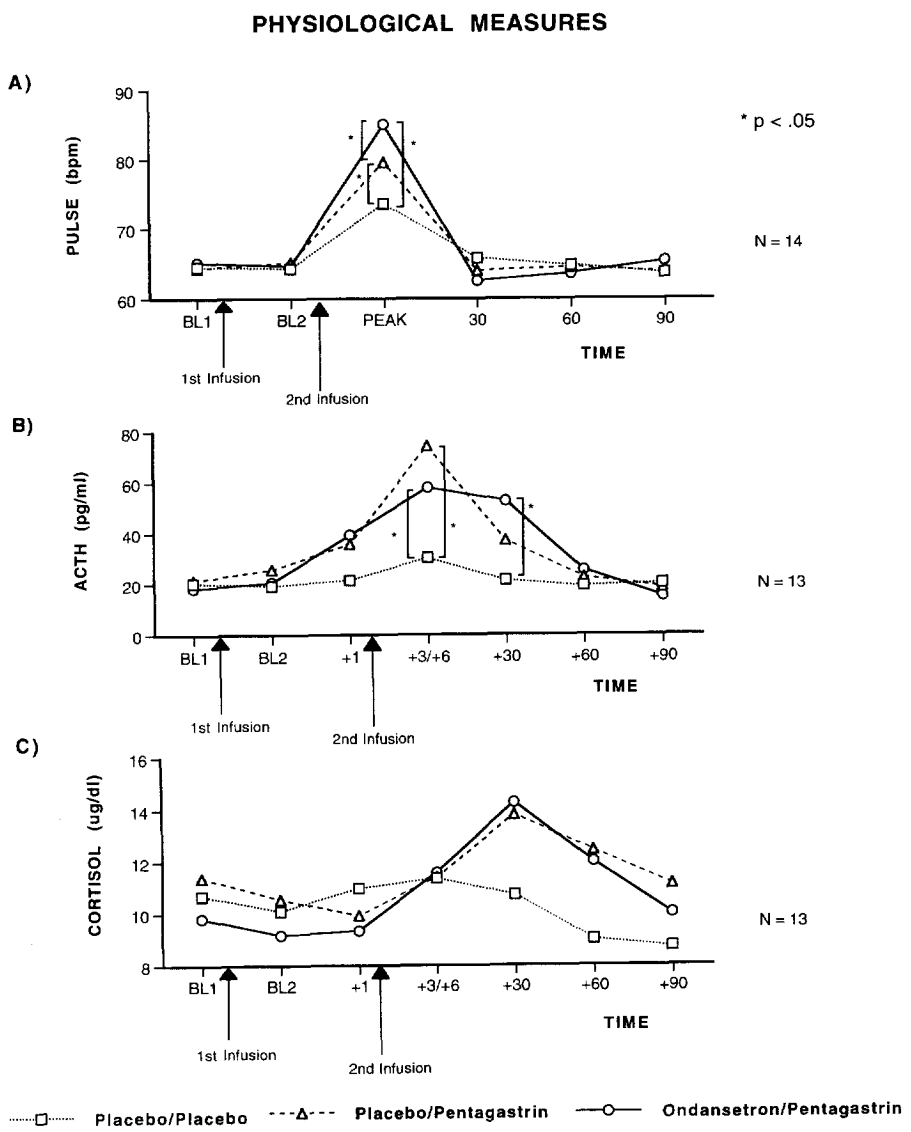

Figure 3. Effects of ondansetron pretreatment on pentagastrin-induced changes in pulse, plasma ACTH, and plasma cortisol in patients with panic disorder and social phobia. Peak measurements are the group mean maximum values during the 5-min social interaction task/infusion procedure. Post measurements indicate the group mean values immediately after the social interaction task.

DISCUSSION

The principal finding of this study is that ondansetron, administered at doses that are effective for antiemesis, does not prevent the anxiogenic effects of intravenous pentagastrin. Rather, ondansetron pretreatment led to nonsignificant increases in pentagastrin-induced anxiety and led to greater levels of nonspecific physical and emotional symptoms during the pentagastrin infusion paradigm. These findings suggest that pentagastrin-induced anxiety and panic are not blocked by 5-HT_3 receptor antagonism.

In contrast to the overall absence of effect seen on behavioral outcome measures, ondansetron did appear to influence physiological variables. In particular, ondansetron pretreatment was associated with greater increases in pulse during the pentagastrin infusion paradigm. Whereas increases in pulse might be related to increased discomfort, they might also be due to actions at vagal 5-HT_3 receptors. Ondansetron also tended to blunt the peak pentagastrin-induced ACTH response, although this trend did not reach statistical significance. Ondansetron pretreatment was associated with a prolonged ACTH response, so that ACTH levels 30 min after pentagastrin administration continued to be greater than those seen in the saline/saline condition. Again, prolonged elevations in ACTH may have been related to increased discomfort and nonspecific stress experienced by subjects during the ondansetron/pentagastrin condition.

As previously found patients with social phobia and panic disorder have similar responses to pentagastrin infusion when pentagastrin is administered in the context of a social interaction task (McCann et al. 1997). Although the social interaction task itself was clearly anxiogenic, pentagastrin was found to produce additional distinct anxiogenic effects. Of the 14 patients participating, five had panic attacks in the placebo/pentagastrin condition (three with panic disorder and two with social phobia), and six had panic attacks in the ondansetron/pentagastrin condition (Four with panic disorder and two with social phobia). These numbers are slightly lower than those reported previously, again suggesting that use of the social interaction task did not lead to false elevations in panic. The characteristics of pentagastrin-induced panic attacks, their similarities to naturally occurring and pharmacologically provoked panic attacks have been previously reported (Abelson et al. 1991; Abelson and Nesse 1994; Abelson et al. 1994; van Megan et al. 1994; McCann et al. 1995, 1997) and will not be re-reviewed here.

It is possible that different dosages or ondansetron regimens might have been more effective in preventing pentagastrin-induced anxiety than that used in the present study. However, since the ondansetron dose used in this study is routinely used for antiemesis, it clearly possesses physiological effects in humans. Notably, ondansetron did not block pentagastrin-induced nausea or stomach discomfort, suggesting that these effects of pentagastrin might be secondary to direct actions of pentagastrin on the gastrointestinal tract, rather than actions at the vagus or in the central nervous system. It remains to be determined whether chronic treatment with ondansetron, such as those reported to be effective in the treatment of panic disorder and social phobia, are more effective in preventing pentagastrin-induced anxiety.

In sum, pretreatment with the 5-HT_3 receptor antagonist, ondansetron, at doses effective for antiemesis, does not attenuate the anxiogenic effects of pentagastrin in patients with panic disorder and social phobia. This observation suggests that pentagastrin-induced anxiety is not mediated via 5-HT_3 receptor agonism. Despite a lack of effect on behavioral indices, ondansetron pretreatment was associated with greater levels of pentagastrin-induced nonspecific physical symptoms, greater pulse rates during the pentagastrin infusion paradigm and alterations in the pentagastrin-induced ACTH response curve. These effects of ondansetron pretreatment might all be attributable to nonspecific stress secondary to increases in physical discomfort in the ondansetron/pentagastrin condition. Mechanisms by which peripherally administered gastrointestinal peptides lead to profound changes in emotional state remain to be elucidated.

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