

Phasic craving for carbohydrate observed with citalopram

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The serotonin selective reuptake inhibitors (SSRIs) have clinically and anecdotally been associated with nausea and weight loss as a side effect of their action. The tricyclic antidepressants have been linked to carbohydrate (CHO) craving and weight gain in patients with major depressive disorders. This side effect has been attributed to the strong anti-histaminergic actions of these agents and is recognized as a causal factor of non-compliance in a substantial percentage of patients. CHO craving is an important feature and complication of the treatment of depression and is often ignored. A total of 18 patients were treated with the SSRI citalopram in our mood disorder clinic. In eight cases there was a significant increase in CHO craving together with weight gain shortly after initiation of treatment. The craving for CHO took on a phasic presentation. These cases are presented, together with data on the change in mood and anxiety symptom rating scales. Our observations appear paradoxical, given that serotonin (5-HT) typically mediates a reduction in CHO intake and that citalopram displays potent and select 5-HT-enhancing actions. However, the receptor binding profile of citalopram may predict a risk for inducing this adverse event. These, together with serotonergic, dopaminergic, histaminergic and other possible mechanisms are discussed. A profound influence on patient acceptability was observed, suggesting that the impact on compliance needs to be considered.

Keywords: Carbohydrate craving – Citalopram – Dopamine – Histamine – SSRI – Weight gain

INTRODUCTION

Fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram, collectively referred to as selective serotonin reuptake inhibitors (SSRIs), have introduced significant advances to the long-term and acute management of depression (Kasper and Heiden, 1995), primarily due to a highly selective action and distinct pharmacokinetic advantages. Tricyclic antidepressants (TCAs) have a non-selective action on biogenic amine and other receptors (Beaumont *et al.*, 1995), resulting in non-specific binding to a range of receptors, viz. muscarinic (mACh), histamine (H)-1 and α_1 -adrenergic receptors leading to the typical TCA-associated side effects. These actions underlie the high incidence of cognitive dysfunction, dry mouth, constipation and visual disturbances due to their strong antimuscarinic actions, cardiovascular instability due to their α -adrenolytic actions, while weight gain and sedation are proposed to be due their anti-histaminergic effects (Beaumont *et al.*, 1995).

Targeted drug design has allowed the SSRIs to widen the concentration gradient between select actions on serotonin (5-HT) uptake and interactions

at the above receptors (Hyttel, 1994). However, interactions at some receptor sites still occur and, due to structural differences, they appear to vary in intensity from one SSRI to the next. Consequently, sertraline and paroxetine display higher binding affinities for mACh receptors while citalopram is characterized by a greater degree of binding to H-1 receptors compared to other SSRIs (Hyttel, 1994; Leonard, 1995). The question arises whether these affinities are clinically relevant. Certainly, paroxetine displays an affinity for mACh receptors similar to imipramine (Richelson, 1994) and has been associated with the highest incidence of antimuscarinic side effects compared to the other SSRIs (Finley, 1994). A higher incidence of sedation, in agreement with a potential antihistaminergic action on arousal mechanisms (Richelson, 1994), appears to occur with citalopram (Finley, 1994). Furthermore, despite an improved side effects profile, the selective action on 5-HT uptake by SSRIs has revealed that these drugs can present with not only non-specific 5-HT-mediated side effects such as nausea, headaches, agitation, etc.

(Beaumont *et al.*, 1995), but also some rare but serious adverse effects such as parkinsonism, dystonia and the serotonin syndrome, which appear to be due to excessive 5-HT-mediated suppression of dopamine (DA) activity in the striatum (Sternbach, 1991; Arya, 1994). In this paper, we review the case material of eight patients seen in our clinic, where we describe for the first time the induction of CHO craving, with associated weight gain, in patients treated for affective disorders with citalopram, a highly potent and selective SSRI (Hyttel, 1994). Possible mechanisms are discussed.

CASE STUDIES

Eight patients who presented to our outpatient anxiety disorder and mood disorder clinics are described herein. None of the patients displayed features of atypical depression, i.e. reverse diurnal rhythm, CHO craving and hypersomnia prior to treatment. Two cases are described and the data of the remainder are

summarized in Table I. Table II presents a week-by-week weight analysis for each patient.

Case 1

A 28-year-old married female presented with a history of depressed mood associated with co-morbid panic attacks. She was initially treated with fluoxetine 20 mg/day but developed agitation and refused further treatment with this agent because of adverse press publicity surrounding its use. She was subsequently treated with citalopram 20 mg/day. After 10 days she reported an increase in finding and seeking behaviour for CHO-rich foods. This was documented to commence at approximately 15.00 h every day. On entry to the treatment programme she was 1.74 m tall and weighed 54 kg. Over 4 weeks of treatment, her body weight increased steadily to reach 62 kg at week 4 (Table II). The Montgomery Asberg Depression Rating Scale (MADRS) dropped from 28 to 20, Hamilton Depression Rating Scale (HAM-D) from 26 to 17 and the Hamilton Anxiety Rating Scale

TABLE I: Case study summaries: patient data, diagnosis, treatment and outcome

Case	Age (years)	Gender	Diagnosis	Citalopram (mg/day)	Δ mass (kg)	Δ CGI	Δ rating score
1	28	F	MDD + anxiety	20	+8.0	5-2	28-20 ¹
2	42	M	PD + agoraphobia	20	+9.0	6-2	34-15 ²
3	18	F	MDD, PD, SP	40	+6.0	6-2	28-16 ¹
4	46	M	MDD, PD + agoraphobia	30	+11.0	7-2	24-14 ¹
5	39	F	MDD + anxiety	40	+5.5	6-2	38-19 ¹
6	38	F	MDD + anxiety	40	+7.0	5-3	29-22 ¹
7	31	F	MDD + anxiety	20	+4.8	5-2	27-12 ¹
8	39	F	MDD + anxiety	20	+5.5	4-2	26-17 ¹

Δ change.

MDD, major depressive disorder; PD, panic disorder; SP, social phobia.

¹MADRS.

²HAM-A.

TABLE II. Patient weekly weight analysis (kg)

Case	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
1	54.0	55.0	57.5	60.0	62.0	Discont.
2	64.0	65.0	68.0	68.5	69.0	73.0
3	49.0	53.0	53.5	54.0	55.0	Discont.
4	77.0	79.5	81.0	86.8	88.0	Discont.
5	69.0	70.5	72.0	72.8	74.5	Discont.
6	58.0	59.5	62.0	63.4	65.0	Discont.
7	67.0	68.0	69.5	71.0	71.8	Discont.
8	81.0	83.0	85.0	85.5	86.8	Discont.

Discont., patient discontinued treatment

(HAM-A) from 32 to 19 (Table I). There was an improvement in Clinical Global Impression (CGI) from 5 to 2 (Table I). Because of her increase in weight, citalopram was stopped on the patient's request and at a 2-week follow-up she had lost 2.4 kg. She was not on a kilojoule-restricted diet or exercise programme.

Case 2

A 1.9-m-tall, 42-year-old married man with panic disorder was referred to the anxiety disorders clinic. Previous pharmacological treatment had included imipramine 150 mg/day, buspirone 10 mg twice daily and clomipramine 150 mg/day. The latter agent was discontinued because of weight gain. He was treated with citalopram 20 mg/day. Baseline weight was 64 kg. After 6 days he complained of CHO craving from 14.00 h, a dry mouth and drowsiness. His body weight increased steadily from 64 kg at the start of week 1 to 69 kg at week 4 (Table II). The MADRS changed from 11 to 9, HAM-D from 14 to 11 and the HAM-A from 34 to 15 (Table I). The CGI improvement changed from 6 to 2 (Table I). Despite his dissatisfaction with the weight increase, he elected to continue with the treatment programme. At the end of week 5 his weight was 73 kg, at which point he initiated his own exercise programme. His weight stabilized. Although citalopram effectively addressed the depressive symptoms, the patient's craving for CHO persisted and at 7-month follow-up he had not attained his pre-treatment weight.

In total, 18 patients in our clinic had received citalopram as monotherapy, with eight of these presenting with symptoms of CHO craving and weight gain. In all cases described, citalopram was administered at the same time each morning. There were no pre-morbid features to suggest the presence of atypical depression or an impulse control disorder. None of the subjects had a history of an eating disorder. An obvious change in weight was noticeable within 7–10 days (Table II). These patients described an intense craving for CHO starting early in the afternoon and persisting until the late evening with a subsequent increase in weight. Except for the patient described in case 2, all the patients requested discontinuation of their medication after 4 weeks. As in case 1, said discontinuation of citalopram resulted in a gradual return to pre-treatment body weight (data not shown). Despite this effect on weight, 4 weeks' exposure to citalopram resulted in a favourable clinical response in both the depressed mood and panic attack frequency, intensity and quality as demonstrated by the CGI and change in HAM-D, HAM-A and

MADRS rating scales. Response to citalopram was relatively rapid with a reduction in clinical symptoms.

DISCUSSION

In this report we present evidence that treatment of mood disorders with the SSRI citalopram may be associated with CHO craving and weight gain in susceptible patients.

Neurochemical studies provide evidence that a host of neurotransmitters and peptides, operating alone or in concert, are involved in the complex central and peripheral regulation of appetite behaviour. These include noradrenaline (NA), DA and 5-HT as well as neuropeptides such as cholecystokinin, corticotrophin releasing factor, neuropeptide Y and opioids (Blundell, 1990; Goldbloom *et al.*, 1991; Lambert *et al.*, 1993). When considering the biogenic amines specifically, the involvement of 5-HT is well recognized (Leibowitz, 1990; Goldbloom *et al.*, 1991). DA involvement is suggested in that phenothiazines and butyrophenones are known to induce weight gain, an effect linked to an increased appetite and rate of eating with DA receptor blockade (Blundell, 1990; Goldbloom *et al.*, 1991). Alpha-2 noradrenergic receptors in the paraventricular nucleus (PVN) of the medial hypothalamus operate in concert with 5-HT to modulate CHO ingestion (Leibowitz, 1990; Goldbloom *et al.*, 1991). Similarly, hypothalamic histamine exerts an inhibitory action on feeding via histaminergic projections to the ventromedial and PVN (Sakata *et al.*, 1990), such that inhibition of histamine results in an inability to detect a low protein diet with resultant weight gain (Mercer *et al.*, 1994).

Reports of persistent weight gain with SSRIs have not been documented. The observations presented in these case studies may reflect two scenarios, i.e. a structurally specific action of citalopram, or a yet unrecognized rare event possible with other SSRIs as well. The biochemical basis for these observations is of great interest but is, at best, speculative, especially since 5-HT has been found to control the ratio of CHO versus protein intake, with 5-HT stimulation being essential in reducing the proportion of CHO in the diet (Leibowitz, 1990). This would predict that the SSRIs, including citalopram, will exert either a reduction, or at best a limited effect, on CHO craving and weight gain. Our observations appear paradoxical, given the potent and selective 5-HT-enhancing action of citalopram (Hyttel, 1994). However, a neurochemical basis for this paradox may involve DA and/or histamine, with 5-HT playing an integral role in the ultimate response.

Although the affinity of citalopram for DA receptors and DA uptake mechanisms are unremarkable (Hytell, 1994), a possible explanation for our results may involve DA. DA blockade is associated with an increase in caloric intake (Goldbloom *et al.*, 1991). The SSRIs, via 5-HT-mediated suppression of DA pathways in the striatum, are rarely associated with symptoms indicative of DA hypofunction, e.g. extrapyramidal effects and dystonia (Arya, 1994). The effect of DA on feeding has been related to "hedonic" eating as part of a reward system (Goldbloom *et al.*, 1991). Anatomically, there is evidence to support such an interaction and 5-HT and DA terminals have been found to converge in the ventrolateral nucleus accumbens (Phelix and Broderick, 1995), the latter nuclei forming part of the DA reward system (Hyman and Nestler, 1996). In support of this, *in vivo* microdialysis studies in rats indicate that fluoxetine, a less potent SSRI, can engender significant suppression of DA accumulation in the nucleus accumbens (Ichikawa and Meltzer, 1995). However, fluoxetine is best known for its anorectic action in humans (Wise 1992; Finley, 1994). Furthermore, studies in obese patients have revealed significant weight-reducing efficacy with high-dose fluoxetine (60 mg/day; Wise, 1992; Goldstein *et al.*, 1994), while a recent citalopram study (60 mg/day) failed to reach a similar conclusion (Szkudlarek and Elsborg, 1993). Obvious differences in 5-HT uptake affinity and 5-HT/NA selectivity between SSRIs have not proved to be clinically relevant (Leonard, 1995) and it is speculative that these differences may predict differential actions on DA function. However, other pharmacological differences in histamine and 5-HT receptor binding are evident. The enantiomers of fluoxetine, but not citalopram, interact stereospecifically with the 5-HT_{1c} receptor (Wong *et al.*, 1991). Interactions with this receptor are implied in the anorectic actions of fluoxetine and arylpiperazine class of 5-HT agonists (Wong *et al.*, 1991). Fluoxetine also appears to act as a 5-HT releaser (Leibowitz, 1990). Among the SSRIs, citalopram presents with the highest affinity for the H1 receptor ($K_i=470$ nM; Richelson and Nelson, 1984; Hytell, 1994). This affinity figure, while still significantly low by TCA standards (e.g. dothiepin $K_i=3.6$ nM, amitriptyline $K_i=1.1$ nM; Richelson and Nelson, 1984), interprets an affinity for the H1 receptor roughly 13 times more potent than fluoxetine ($K_i=6200$; Richelson and Nelson, 1984). However, do these *in vitro* data translate into clinically relevant side effects?

Although the stimulatory action on CHO ingestion induced by HA-1 blockade can be demonstrated in

rats (Sakata *et al.*, 1990; Mercer *et al.*, 1994; Tuomisto, 1994), such a cause and effect relationship appears more complex in humans. Still, this mechanism has been cited as the reason for the weight increase seen with certain TCAs (Richelson, 1994; Beaumont *et al.*, 1995). However, pure H1 antagonists, with the exception of phenothiazine derivatives, are not associated with weight gain (McEvoy, 1991). Cyproheptadine is the exception, having an ability to increase CHO intake in both rats and humans with an associated increase in weight (Leibowitz, 1990; Sanders-Bush and Mayer, 1996). However, cyproheptadine is not only an H1 antagonist, but also blocks 5-HT₂ receptors (Sanders-Bush and Mayer, 1996). Citalopram and trazodone ($K_i=350$ nM) display similar dissociation constants for the H1 receptor (Richelson and Nelson, 1984). The latter has been associated with weight gain in clinical studies (Marek *et al.*, 1992; Weisler *et al.*, 1994). However, as with cyproheptadine, the effects of trazodone on weight may involve both an H1 and 5-HT₂ antagonistic profile (Marek *et al.*, 1992). This combined action seems necessary since pooled analysis of placebo-controlled trials of nefazodone, a chemically and pharmacologically related agent with similar 5-HT₂ blocking action but insignificant H1 blockade (Preskorn, 1995), revealed no changes in weight between nefazodone and placebo (Physicians Desk Reference, 1995). Although citalopram does not block 5-HT₂ receptors (Hytell, 1994), acute administration of citalopram (or any SSRI) may be expected to induce an initial suppression of 5-HT release, and a reduction in 5-HT₂ receptor stimulation, due to a compensatory presynaptic action by 5-HT_{1A} autoreceptors to reduce the sudden increase in 5-HT activity (Goodwin, 1996). This together with an acute H1 block, may engender a response analogous to that seen with cyproheptadine. This acute effect is expected to wane over a few weeks due to desensitization of 5-HT_{1A} receptors resulting in increased stimulation of 5-HT₂ receptors. We were not able to confirm this since all but case 2 opted to discontinue citalopram after 4 weeks. An interesting observation of the present study was that all the subjects experienced a phasic craving for sweetness, suggesting that circadian feeding patterns, where ingestion of CHO-rich food is usually under strict 5-HT control in the medial hypothalamus (Leibowitz, 1990), may be suppressed through disruption of ventromedial HA/5-HT function by citalopram.

In conclusion, this paper emphasizes a potential risk of weight gain, related to an increased craving for CHO, in patients receiving citalopram. These observations were noted during acute treatment (within 4

weeks). The underlying mechanisms need to be investigated further, and whether these acute effects do, in fact, disappear over long-term use. This may have significant clinical relevance, especially in depressed patients, as well as those suffering from eating disorders such as bulimia nervosa, where an obsession with weight may lead to non-compliance. In addition, there are distinct compliance considerations in depressed patients who are already obese, or those who have pre-established problems with weight management. However, this same property may be desirable in the treatment of co-morbid depression in patients suffering from anorexia nervosa where an anorectic action may be counter-productive, or when marked weight loss is associated with depression. Clearly, controlled comparative clinical trials need to be undertaken to access these assumptions in the above populations.

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