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PLASMA BROMOCRIPTINE LEVELS, CLINICAL AND GROWTH HORMONE RESPONSES IN PARKINSONISM

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1 Plasma bromocriptine levels following separate oral doses of bromocriptine 12.5 25, 50 and 100 mg have been determined in ten subjects with parkinsonism.

2 There was considerable variation between peak plasma bromocriptine levels in individual subjects after similar doses of bromocriptine. Peak levels occurred 30–210 min after dosage (mean 102 min). Peak clinical response, peak rise in plasma growth hormone level and fall in blood pressure followed shortly after peak bromocriptine levels occurred.

3 The shape of the plasma-time curve for bromocriptine was similar with all dosages.

4 There was no significant relationship between peak plasma bromocriptine levels, peak clinical response, peak increase in growth hormone and peak fall in blood pressure. However, the degree of improvement in the signs of parkinsonism was related to plasma bromocriptine levels achieved.

5 Metoclopramide 60 mg pretreatment had no consistent effect upon plasma bromocriptine levels, the clinical or hormonal response.

Introduction

Bromocriptine causes behavioural and hormonal changes which last for several hours after giving a single dose (Johnson, Vigouret & Loew, 1974). Motor hyperactivity in animals, suppression of hyperprolactinaemia in man, and improvement in parkinsonism following bromocriptine, all last approximately 6–8 h (Snider, Hutt, Stein, Prasad & Fahn, 1976; Brun del Re, del Pozo, Grandi, Friesen, Hinselmann & Wyss, 1973; Calne, Teychenne, Claveria, Eastman, Greenacre & Petrie, 1974), and in acromegalics, suppression of growth hormone (HGH) levels lasts for a similar period (Liuzzi, Chiodini, Botalla, Cremascoli, Müller & Silvestrini, 1974). All these changes are attributable, directly or indirectly, to dopamine receptor stimulation.

The behavioural and hormonal effects that follow a single dose of levodopa are similar in nature to those that follow bromocriptine, but last only 1–2 h. Because of the prolonged action of bromocriptine, it has certain theoretical advantages over levodopa in the treatment of Parkinson's disease, hyperprolactinaemia and acromegaly. The magnitude of clinical response in Parkinson's disease is often, but not always, associated with the magnitude of the peak plasma dopa level, and fluctuations in clinical response are often associated with fluctuations in plasma dopa levels (Shoulson, Glaubiger & Chase, 1975). To see whether this is also the case with bromocriptine, we have determined plasma bromocriptine levels, clinical response and changes in plasma HGH concentration after giving single oral doses of bromocriptine to patients with Parkinson's disease. Metoclopramide is commonly given in association with bromocriptine or levodopa to prevent emesis. We have determined the effect of metoclopramide pretreatment upon plasma bromocriptine levels and clinical response.

Methods

Patients

Ten patients with Parkinson's disease, eight men and two women, aged 57–68 (mean age 61) years were studied. All these patients were moderately or severely disabled, and all had bilateral rigidity, akinesia and tremor with a postural and gait deformity. They had previously been treated with levodopa, amantadine and/or anticholinergic drugs for 2–12 years. These patients were selected for this study by their ability to tolerate bromocriptine without developing nausea, vomiting, hallucinations or symptomatic postural

hypotension, and showed a favourable clinical response to bromocriptine.

Determinations

The detailed protocol used to determine clinical and hormonal responses to single oral doses of antiparkinsonian drugs is described elsewhere (Debono, Marsden, Asselman & Parkes, 1976). The following measurements were made under standardized conditions, before and after an oral dose of bromocriptine:

(1) Clinical disability score:- determined as the sum of separate tremor, akinesia, rigidity and postural deformity scores on a 0–12 scale (0=no disability, 12=maximum disability).
(2) The presence or absence, type and severity of dyskinesias.
(3) The presence or absence of nausea and vomiting.
(4) The standing and lying blood pressure. Mean arterial pressure (MAP) was derived as follows: diastolic + 1/3 pulse pressure.
(5) Plasma HGH concentration (ng/ml).
(6) Plasma bromocriptine concentration (ng/ml).

These clinical measurements were determined and blood samples taken at 30 min intervals over a 5 h period, commencing 1 h before bromocriptine was given. Blood was taken through an indwelling forearm venous catheter.

Treatment

All patients received bromocriptine at 09.30 h by mouth. Different doses (12.5 25, 50 or 100 mg) were given on separate occasions at 1 week intervals. Three patients were given a single bromocriptine dose, one patient was given two different doses, four patients were given three doses, and two patients four doses. No other drugs were given in this part of the study. On separate occasions, metoclopramide 60 mg was given 1 h before bromocriptine 12.5, 25, 50 or 100 mg. Two patients were given a single dose of bromocriptine, two patients two different doses, one patient three doses and one patient four doses.

No antiparkinsonian drug was given for 24 h before each study, and the last dose of bromocriptine was given 36 h before study. All subjects were fasted until breakfast was given immediately prior to bromocriptine administration.

Plasma bromocriptine and growth hormone levels

Plasma bromocriptine was determined by radioimmunoassay. The competitive inhibitory potency of bromocriptine was used to inhibit the reaction between antibody directed against 9,10–dihydro–α–ergokryptine and heavily labelled 9,10–dihydro–α–ergokryptine–(13-^{3}H). This compound has a specific radioactivity of 21.3 mCi/mg (R. Voges, 1976 unpublished results). Sheep were immunised by employing an emulsion of Freund's adjuvant containing albumin 9,10–dihydro–α–ergykryptine–conjugate. The antiserum obtained combines preferentially with the structures of the intact peptide moiety of the ergot peptide alkaloid and has much less affinity for the tetracyclic structural elements of the 2–bromolysergic acid part. Obviously, metabolites are not likely to interfere, and there was some evidence that only parent drug is being assayed. Detection was limited to 0.25 mg active compound /ml plasma. The standard curve employing bromocriptine was in the range of 0.3–5.2 ng alkaloid base /ml plasma. Random analytical error (precision) was calculated by the distribution of replicate measurements around the mean and amounted to approximately 3%. The systematic analytical error (accuracy) to reproduce the standard curves with regard to slope and intercept amounted to approximately 10%.

Side effects

Side effects during the conduct of the trial were few. No patient became confused, hallucinated or had any mood disturbance after the administration of bromocriptine. Symptomatic postural hypotension but no loss of consciousness occurred in one subject after a single bromocriptine dosage (12.5 mg, but not higher dosages), and two subjects were nauseated but did not vomit after bromocriptine 50 mg.

Results

Plasma bromocriptine levels

Mean plasma bromocriptine levels (± s.e. mean) at 30 min intervals for 4 h following standard oral doses of 12.5 mg, 25 mg, 50 mg and 100 mg in subjects with parkinsonism are shown in Figure 1. Peak plasma bromocriptine levels occurred 30–210 min after dosage (mean time of peak levels, 102 ± 9.6 min). In most subjects, peak plasma bromocriptine levels occurred about 90 min after bromocriptine 12.5, 25 and 100 mg and 120 min after bromocriptine 50 mg.

The shape of the bromocriptine plasma-time curve was similar in most subjects and at different dosages. There was an initial rapid rise in plasma bromocriptine concentration with a subsequent slower fall. Plasma bromocriptine levels at 4 h were approximately three quarters peak values.

Following bromocriptine 12.5, 25, 50 and 100 mg by mouth, mean peak plasma levels were as shown in Table 1. Three subjects had however peak plasma

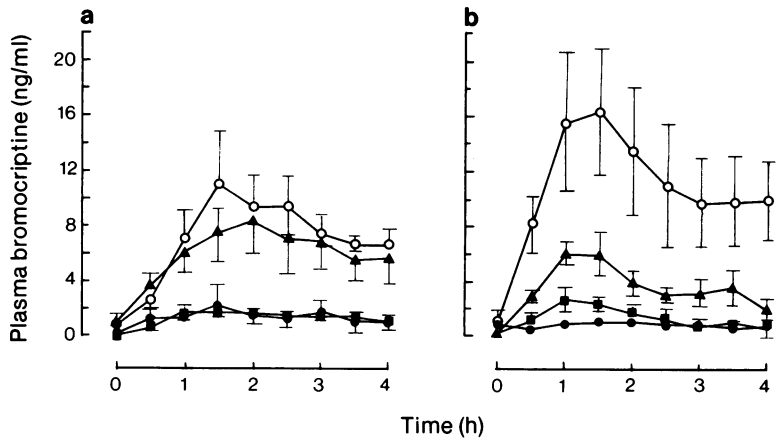

Figure 1 Plasma bromocriptine levels (±1 s.e. mean), (a) at 30 min intervals after oral dosages of bromocriptine 12.5 (■), 25 (●) 50 (▲) and 100 (○) mg, and (b) with metoclopramide pretreatment given 30 min before bromocriptine.

bromocriptine levels following 25 mg than following 12.5 mg and one patient had a lower level after 100 mg than after 50 mg.

There was a considerable variation in peak plasma bromocriptine levels in different patients following the same bromocriptine dosage. The range of peak plasma bromocriptine levels in different subjects following bromocriptine 12.5, 25, 50 and 100 mg was 1.3–5.3 ng/ml, 1.4–3.5 ng/ml, 2.6–19.7 ng/ml and 6.5–24.6 ng/ml, respectively.

On 9 out of 24 occasions in 5 out of 10 subjects on regular treatment with bromocriptine in a dosage of between 12.5 and 150 mg daily, bromocriptine was detected in fasting blood samples as a result of previous treatment.

Plasma bromocriptine levels with metoclopramide pretreatment

The effect of giving metoclopramide 60 mg 30 min before bromocriptine upon plasma bromocriptine levels is shown in Figure 1 and Table 1. In some, but not all subjects, there was a slight increase in peak plasma bromocriptine levels following metoclopramide pretreatment, as compared with bromocriptine alone. Peak plasma bromocriptine levels occurred slightly earlier following metoclopramide pretreatment (with all dosages, mean peak levels occurred at 78 ± 52 min) compared with bromocriptine alone (102 ± 9.6 min).

Relation between plasma bromocriptine levels, clinical and hormonal responses

Antiparkinsonian actions:- The clinical response to bromocriptine with and without metoclopramide pretreatment is shown in Table 1. Improvement in the signs of parkinsonism was evident within 30–90 min of giving bromocriptine, and maximum improvement occurred at 130 ± 12 min, approximately 30 min after the mean time of peak bromocriptine levels. In most patients, the improvement in parkinsonian disability persisted throughout the trial period.

In most subjects, the clinical response to bromocriptine was slightly greater with higher bromocriptine dosages than with lower dosages. Two patients, however, had a lesser clinical response to bromocriptine 100 mg than to 12.5 mg and 25 mg, although in these subjects, higher peak plasma bromocriptine levels occurred following 100 mg than following lower dosages.

There was a statistically significant relationship between plasma bromocriptine levels and concurrent changes in clinical response compared with pretreatment scores ($r=0.395$, $n=162$, $P<0.001$). However, there was no significant relationship between the magnitude of peak plasma bromocriptine level and the magnitude of the peak clinical response (Figure 2). Two subjects had a good clinical response (30–50% reduction in total disability score) with low peak plasma bromocriptine levels (less than 2 ng/ml) and on separate occasions, a poor clinical response (0–30% reduction) with high peak plasma bromocriptine levels (4–8 ng/ml).

Metoclopramide pretreatment resulted in some subjects in a minor reduction in clinical response at all bromocriptine dose levels, despite slight and inconstant increases in peak plasma bromocriptine levels (Table 1).

Involuntary movements Involuntary movements, chorea, orofacial dyskinesia and dystonic postures of

Table 1 Mean peak plasma bromocriptine levels, peak clinical response and proportion of patients with a HGH rise greater than 3 ng/ml following bromocriptine 12.5, 25, 50 and 100 mg, alone, and following metoclopramide 60 mg pretreatment.

	Bromocriptine											
	12.5 mg			*25 mg*			*50 mg*			*100 mg*		
	Mean	*s.e. mean*	*Range*	*Mean*	*s.e. mean*	*Range*	*Mean*	*s.e. mean*	*Range*	*Mean*	*s.e. mean*	*Range*
Peak plasma bromocriptine level (ng/ml)	2.9	± 0.8	1.3–5.3	2.4	± 0.3	1.4–3.5	9.3	±2.3	2.6–19.7	12.1	±3.4	6.5–24.6
After metoclopramide 60mg	1.0	—	—	3.0	± 0.6	1.8–3.4	7.4	±0.8	6.0–8.9	17.4	±4.0	13.2–25.4
Peak % reduction in clinical disability (score units)	26.8	±12.5	0–6	18.0	±5.2	0–55	34.6	±5.3	20–63	37.0	±8.4	9–58
After metoclopramide 60mg	18.0	—	—	14.7	±12.7	0–40	10.2	±4.2	2–27	14.5	±4.1	3–21
Peak reduction in supine MAP (mmHg)	16.4	± 4.6	0–25	21.0	±3.4	10–34	23.1	±5.4	6–50	20.3	±9.3	7–35
After metoclopramide 60mg	13.0	—	—	24.0	± 9.7	11–43	14.2	±7.7	0–41	20.5	±5.7	10–35
Peak reduction in erect MAP (mmHg)	12.0	±6.1	—3–30	12.7	± 3.9	0–30	27.7	±7.0	7–47	25.3	±7.8	7–35
After metoclopraminde 60mg	27.0	—	—	20.0	±13.0	7.33	18.2	±7.7	2–46	28.5	±8.1	13.50
Proportion of patients with HGH rise greater than 3 ng/ml		0/3			1/6			3/6			3/5	
After metoclopramide 60mg		0/1			0/2			1/4			2/4	
Proportion of patients with dyskinesias		0/4			4/9			4/7			2/5	
After metoclopramide 60mg		1/1			0/3			1/5			0/4	
Proportion of patients nauseated		0/4			0/9			2/7			0/5	
After metoclopramide 60mg		0/1			0/3			0/5			0/4	

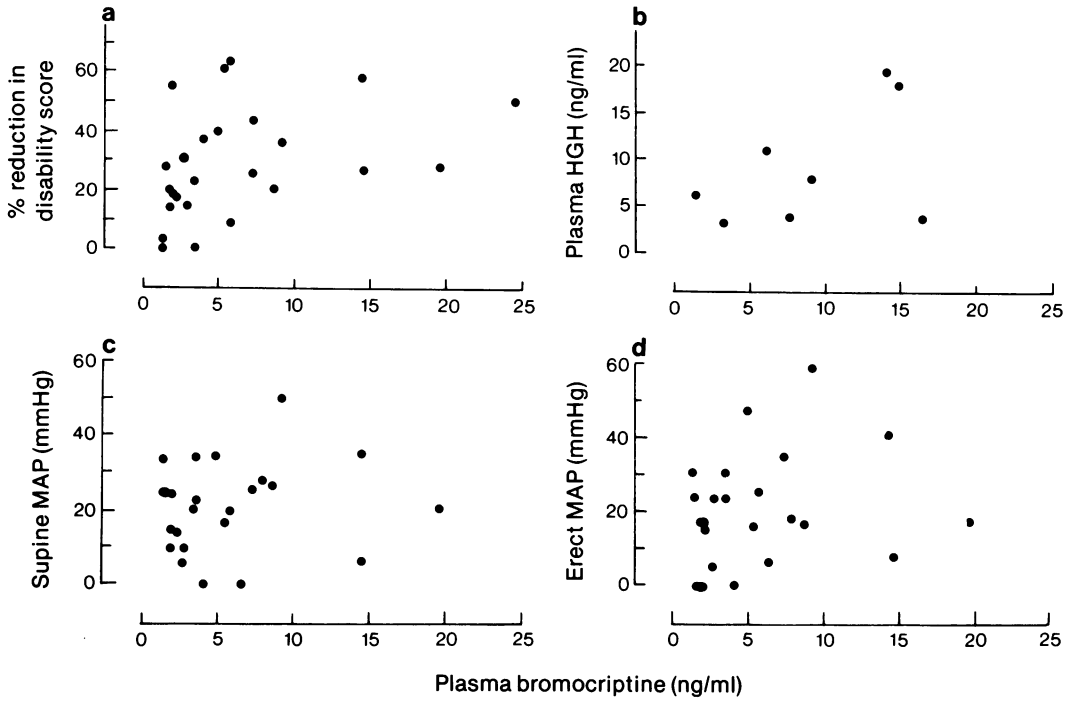

Figure 2 Peak plasma bromocriptine levels achieved at all dosages given in ten patients and (a) corresponding peak % reduction in parkinsonian disability, (b) rise in plasma HGH level, and reduction in (c) lying and (d) standing MAP, as compared with baseline levels. Correlation coefficients, r as follows (a) 0.40, $P<0.001$; (b) 0.14, $P>0.05$ NS; (c) 0.10, $P>0.05$ NS; (d) 0.15, $P<0.05$.

the trunk and limbs occurred in five or ten patients given bromocriptine. Dyskinesias appeared within 90–180 min of oral dosage with bromocriptine, and at approximately the same time as peak plasma bromocriptine levels occurred. Dyskinesias were of greater severity and of longer duration in two subjects given bromocriptine 50 and 100 mg than in the same subjects following 12.5 and 25 mg, although in all subjects with dyskinesias, there was no obvious relationship between plasma bromocriptine levels and the severity of dyskinesias. In subjects with dyskinesias, mean peak plasma bromocriptine levels were similar to the levels which occurred in subjects without dyskinesias. On the whole, subjects with bromocriptine-dyskinesias were more disabled than subjects without dyskinesias. In three of the five subjects with dyskinesias, pretreatment with metoclopramide abolished involuntary movements.

Nausea and vomiting Nausea occurred in two subjects following bromocriptine 50 mg. Nausea was of sudden onset, and lasted 10–15 min. In nauseated subjects, peak plasma bromocriptine levels were no higher than in subjects without nausea. Peak plasma bromocriptine levels occurred at approximately the same time after oral dosage in both nauseated and non-nauseated subjects.

Blood pressure Bromocriptine caused a fall in mean arterial pressure (MAP) in both the standing and lying posture in most but not all subjects with parkinsonism (Table 1). The fall in blood pressure produced symptomatic hypotension in only one subject. On average, the maximum fall in blood pressure occurred 30 min after the initial peak clinical response and approximately 60 min after peak plasma bromocriptine levels occurred.

There was no statistically significant relationship between the peak plasma bromocriptine levels and the maximum fall in either standing MAP or lying MAP ($r=0.127$, $n=24$, $P>0.05$, NS, and $r=0.235$, $n=24$, $P>0.0.05$, NS, respectively). However, considering plasma bromocriptine levels at all measurements, there was a significant relationship between plasma bromocriptine levels and concurrent changes in standing but not lying MAP ($r=0.149$, $n=193$, $P<0.05$, and $r=0.101$, $n=192$, $P>0.05$, NS, respectively).

The fall in blood pressure following metoclopramide pretreatment was comparable to that following bromocriptine alone, in most but not all subjects.

Growth hormone There was some variation in pretreatment plasma HGH levels (0–19 ng/ml). A rise in plasma HGH concentration greater than 3 ng/ml occurred on 7 of 20 occasions in five parkinsonian patients given bromocriptine 12.5–100 mg. Five subjects did not show such an increase in plasma HGH level following any bromocriptine dosages. In subjects with a HGH response, the mean time of peak plasma HGH levels was 173 min after oral bromocriptine dosage, approximately 70 min after peak bromocriptine levels and 40 min after the peak clinical response was achieved. There was no significant relationship between plasma bromocriptine levels and concurrent plasma HGH levels ($r=0.072$, $n=162$, $P>0.05$, NS) or between peak plasma bromocriptine levels and peak plasma HGH levels ($r=0.138$, $n=20$, $P>0.05$, NS)

A rise of plasma HGH greater than 3 ng/ml occurred on 3 out of 11 occasions in two of four patients who received bromocriptine following metoclopramide pretreatment.

Dyskinesias of approximately equal severity occurred both in subjects with a rise in plasma HGH following bromocriptine and in others who did not have a rise in plasma HGH level. The two subjects with nausea following bromocriptine did not have a rise in plasma GH concentration.

Discussion

Following a single dose of bromocriptine, plasma bromocriptine levels increase rapidly to peak values at approximately 100 min and remain elevated for several hours. Bromocriptine has been determined in the plasma of subjects with parkinsonism for up to 12 h after the last oral intake during chronic therapy (Ringwald & Rosenthaler, 1977, unpublished results). Bromocriptine is rapidly absorbed from the gastro-intestinal tract in man and in animals. The major route of elimination is biliary (Nimmerfall & Rosenthaler, 1973, unpublished results) and the pattern of the metabolites excreted either in the bile or in the urine is extremely complex (Kiechel, 1974, unpublished results). It is still not clear to what extent the dopamine stimulant effect of bromocriptine may depend upon active metabolites. The specificity of the antiserum used to assay bromocriptine is preferentially directed toward the peptide part (see Figure 3) of the ergot peptide alkaloid, and it seems established that only parent drug is being detected by this method.

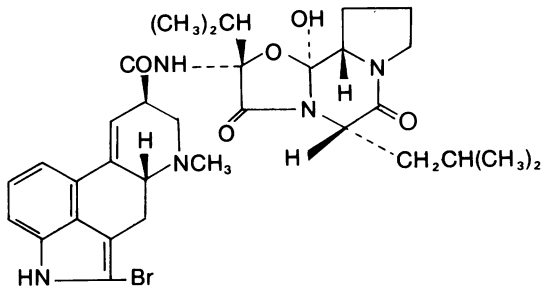

Figure 3 Structural formula of bromocriptine (2-bromo-α-ergokryptine). The antiserum used to determine parent drug is specific to the peptide part (right hand side) of the molecule.

The long period during which bromocriptine can be determined in the plasma corresponds well to the reported time course of activation of dopamine receptors by the drug. In animals, bromocriptine causes stereotyped, rotational behaviour and an increased locomotor hyperactivity for up to 8 h after a single dose (Fuxe, Goldstein, Hökfelt, Jonsson & Lidbrink, 1974). This is in contrast to the shorter period of action of apomorphine and levodopa, both of which have shorter half-lives. Also in human parkinsonism, bromocriptine has a more prolonged effect than levodopa after a single oral dose (Calne *et al.*, 1974), and, in patients with severe dose-related changes in response to multiple oral doses of levodopa, bromocriptine given in separate dosages at similar time intervals may cause a more stable response than following levodopa (Debono, Donaldson, Marsden & Parkes, 1975). In animals, bromocriptine causes an initial phase of inhibition of movement lasting about 1 h before increased mobility occurs (Johnson *et al.*, 1976): a similar phenomenon has not definitely been observed in man.

Bromocriptine, given to humans with hyperprolactinaemia, causes a sustained reduction in prolactin levels (del Pozo, Brun del Re, Varga & Friesen, 1972). This reduction has been attributed to sustained stimulation of pituitary dopamine receptors. Bromocriptine also causes a sustained fall of plasma HGH levels in acromegalics, possibly owing to a direct dopamine-stimulant action on the pituitary somatotroph (Verde, Oppizi, Colussi, Cremascoli, Botalla, Müller, Silvestrini, Chiodini & Liuzzi, 1976). However, the elevation of plasma HGH levels following bromocriptine in normal and parkinsonian subjects is of short duration, 60–90 min only. Elevation of plasma growth hormone levels in normal subjects following levodopa and other dopamine stimulants is likely to be due to the release of growth

hormone releasing factor from hypothalamic dopamine-sensitive peptide neurones (Martin, 1973). This may be dependent on changes in plasma and brain levels of dopamine-stimulants, rather than a sustained elevation in level.

There is a considerable variation in the peak plasma bromocriptine levels achieved after a standard oral dose, and at 4 h after dosage, there may be a five-fold variation in level in different parkinsonian subjects. Variations in absorption and the rate of elimination of bromocriptine may partially explain the variation in clinical response to bromocriptine, for although some parkinsonian patients do well on low bromocriptine dosages (10–20 mg daily), others, who are no more disabled, respond only to high dosages (100 mg daily). There was, however, no direct correlation between peak plasma bromocriptine levels and the magnitude of the peak clinical response in parkinsonism. In those subjects studied, clinical response and plasma bromocriptine levels were both fairly stable over a 4 h period.

Metoclopramide pretreatment occasionally resulted in higher plasma bromocriptine levels than without such treatment, and peak bromocriptine levels occurred slightly earlier following metoclopramide pretreatment. This increase in bromocriptine level in the blood did not always occur, although in two subjects on the higher bromocriptine dosages (50–100 mg) there was a doubling of peak plasma bromocriptine level following metoclopramide. Despite this increase in plasma bromocriptine level, the clinical and HGH response in these subjects was no greater than the response following bromocriptine without metoclopramide pretreatment. This observation is in keeping with the concept that metoclopramide may block nigro-striatal and hypothalamic dopamine receptors. Despite the ability of metoclopramide to block central dopamine receptors, including those of the vomiting centre, in most subjects metoclopramide 10–60 mg daily will prevent nausea due to bromocriptine without greatly reducing the antiparkinsonian response.

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