Piloerection induced by replacing fluvoxamine with milnacipran

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Aims

To present a case of piloerection after replacing fluvoxamine maleate with milnacipran hydrochloride, and to analyse this effect based on receptor occupancy theory.

Methods

A 40-year-old female with a 3-year history of panic disorder was prescribed fluvoxamine 50 mg day⁻¹ in addition to clorazepate dipotassium and sulpiride. Depression was not improved and she complained of fatigue, lack of energy and drowsiness. These symptoms worsened within a few days of an increase in the dose of fluvoxamine to 50 mg twice daily. Since an interaction between fluvoxamine and tizanidine, prescribed by another clinic, was suspected, fluvoxamine was replaced with milnacipran 50 mg day⁻¹. Although her drowsiness improved, she complained of piloerection throughout her body. This symptom gradually abated within a week and when the dosage of milnacipran was increased to 100 mg day⁻¹ at 2 months, no further piloerection occurred. We calculated the changes in α_1 -adrenoceptor occupancy by endogenous norepinephrine during treatment with the usual doses of milnacipran, fluvoxamine and imipramine by using pharmacokinetic and pharmacodynamic parameters obtained from the literature.

Results

The ratios of α_1 -adrenoceptor occupancy by endogenous norepinephrine during the treatment with milnacipran, fluvoxamine and imipramine to that without drug were estimated to be 7.13, 1.00 and 4.12, respectively. The α_1 -adrenoceptor occupancy by endogenous norepinephrine was increased in a dose-dependent manner by milnacipran, whereas fluvoxamine had essentially no effect.

Conclusions

The piloerection observed after the replacement of fluvoxamine with milnacipran in this patient appears to have been due to an increase in the α_1 -adrenoceptor occupancy by endogenous norepinephrine induced by milnacipran.

Introduction

Milnacipran hydrochloride, a serotonin/norepinephrine reuptake inhibitor (SNRI), and fluvoxamine maleate, a selective serotonin reuptake inhibitor (SSRI), are used in the treatment of depression [1]. Both drugs have quite

low affinity for neuroreceptors that do not mediate antidepressant effects, such as histamine-H₁ receptor, α_1 -adrenoceptor and muscarinic acetylcholine (mACh) receptor, so that they rarely induce side-effects mediated by these receptors. In contrast, tricyclic antidepressants,

such as imipramine and desipramine, are well known to cause a wide range of adverse reactions by the blockade of these receptors [2].

Here, we present a case of piloerection associated with replacement of fluvoxamine with milnacipran in a 40-year-old patient with depression. This is the first report of piloerection associated with milnacipran. Piloerection is induced by contraction of the arrector pili muscles following the activation of α_1 -adrenoceptor, and is not attributable to the blockade of neuroreceptors [3]. Indeed, α_1 -adrenoceptor agonists such as midodrine and methoxamine have been reported to induce piloerection [4, 5]. There are few reports of piloerection induced by conventional antidepressants such as tricyclic antidepressants, conceivably because they do not stimulate, but inhibit α_1 -adrenoceptors. On the other hand, milnacipran shows low potential for α_1 -adrenoceptor inhibition and inhibits reuptake of endogenous norepinephrine into the nerve terminals, so that milnacipran may increase the concentration of endogenous norepinephrine in the synaptic cleft and lead to piloerection.

The profiles and frequencies of adverse events are different between milnacipran and fluvoxamine. To characterize and evaluate quantitatively the adverse effects of antidepressants based on their mechanisms of action, receptor occupancy is one of the useful indices [6]. In particular, since these antidepressants have opposite actions, i.e. stimulation and inhibition of α_1 -adrenoceptor, quantitative model analysis using receptor occupancy theory is considered to be useful to predict their adverse reactions. Here, we present the first case of milnacipran-induced piloerection and calculate the α_1 -adrenoceptor occupancy by endogenous norepinephrine as an index of occurrence of drug-induced piloerection, in the presence of milnacipran, fluvoxamine or imipramine in order to explain the mechanism of milnacipran-induced piloerection.

Case report

A 40-year-old female with a 3-year history of panic disorder beginning immediately after a rear-end car collision had been prescribed clorazepate dipotassium 7.5 mg twice daily and sulpiride 50 mg twice daily from a psychiatric clinic for her depression. She had whiplash injury in another rear-end car collision. Loxoprofen sodium 60 mg three times daily, tizanidine hydrochloride 1 mg three times daily, mecobalamin 250 μ g three times daily, rebamipide 100 mg three times daily and felbinac patch (70 mg) twice daily were prescribed from an orthopaedic clinic. In June 2004, fluvoxamine maleate 25 mg twice daily was added for depression, and lorazepam (0.5 mg) was also prescribed to control

anxiety attacks on an as-needed basis. Her depression did not improve and she began to complain of fatigue, loss of energy and drowsiness. Two weeks later, the dosage of fluvoxamine maleate was increased to 50 mg twice daily, but her symptoms worsened within a few days: she could not stand up straight due to dizziness. Although clorazepate dipotassium was replaced with lorazepam 0.5 mg twice daily, her symptoms did not improve. At that time, it was reported that fluvoxamine increases the total AUC and the peak plasma concentration of tizanidine 33-fold and 12-fold, respectively, resulting in hypotension and drowsiness [7]. This interaction is considered to be due to the inhibition of CYP1A2, the primary enzyme for tizanidine metabolism, by fluvoxamine [7, 8]. Following this report, fluvoxamine was replaced with milnacipran hydrochloride 25 mg twice daily, which is not metabolized by CYP1A2 [9], and her drowsiness and fatigue were improved. However, she complained that piloerection was induced throughout her body soon after the initiation of milnacipran and lasted for at least 5 days. A month later she visited our pharmacy and mentioned that piloerection had gradually abated within a week and completely disappeared within a month, and piloerection did not occur again, although the dose of milnacipran hydrochloride was increased to 50 mg twice daily a month later. She was not taking drugs that have been reported to induce piloerection. The Naranjo probability scale [10] indicated that milnacipran was the 'probable' cause of this patient's piloerection.

Methods

Pharmacokinetic/pharmacodynamic analysis

Pharmacological piloerection is considered to be induced by contraction of the arrector pili muscles following α_1 -adrenoceptor stimulation, which is similar to the mechanism of physiological piloerection [3]. Therefore, we considered that the occurrence of piloerection associated with the use of milnacipran and other antidepressants, such as fluvoxamine and imipramine, could be assessed in terms of their effects on α_1 -adrenoceptor occupancy by endogenous norepinephrine, by means of the following procedure.

Pharmacokinetic and pharmacodynamic parameters of antidepressants

The maximum plasma concentrations ($C_{\max}$) and plasma unbound fractions (f_u) of milnacipran, fluvoxamine and imipramine after single-dosage regimens (25 mg p.o.) were obtained from the literature [11–13] (Table 1). In the case of imipramine, the pharmacokinetic parameters of its active metabolite, desipramine, were also collected

Table 1

Pharmacokinetic parameters of milnacipran, fluvoxamine and imipramine obtained from the literature

Drug	Dose (mg)	C _{max} (nm)	f _u	Cf (nm)	Kn, Kn' (nm)	Kd, Kd' (nm)
Milnacipran	25	304	0.626	190	31.0	>10 000
Fluvoxamine	25	28.7	0.270	7.76	1360	1100
Imipramine	25	38.2	0.145	5.54	18.0	85.0
Desipramine*		9.9	0.185	1.83	0.550	130

C_{max}, Maximum plasma concentration; f_u, plasma unbound fraction; Cf, maximum free plasma concentration; Kn, Kn', inhibitory constants for norepinephrine reuptake; Kd, Kd', dissociation constants for α₁-adrenoceptor. *Pharmacokinetic parameters of desipramine are those obtained after oral administration of 25 mg of imipramine.

[14]. The maximum free plasma concentration (Cf) of each drug, the product of C_{max} and f_u, was used as a putative drug concentration in the synaptic cleft. The *in vitro* inhibitory constants for norepinephrine reuptake sites (Kn, Kn') and the *in vitro* dissociation constants for α₁-adrenoceptor (Kd, Kd') for these drugs were also taken from the literature [15–18] (Table 1).

Estimation of the change in norepinephrine concentration in the synaptic cleft by the inhibition of norepinephrine reuptake

We assumed that norepinephrine is secreted from nerve terminals into the synaptic cleft at a constant rate of K_{sec}, and taken up into nerve terminals with a first-order rate constant of k_{uptake}.

Then, the concentration of norepinephrine in the synaptic cleft, C_s, can be determined by Equation 1.

$$\frac{dC_s}{dt} = Ks - k_{\text{uptake}} \cdot C_s \quad (1)$$

where Ks is a quotient of K_{sec} by the volume of synaptic cleft.

Assuming the steady state, the following equations can be obtained by equating the left side of Equation 1 to zero.

$$Ks = k_{\text{uptake}}^{\circ} \cdot C_s^{\circ} \quad (2)$$

$$Ks = k_{\text{uptake}}^{*} \cdot C_s^{*} \quad (3)$$

where C_s[°] and C_s^{*} are the concentrations of norepinephrine in the synaptic cleft at the steady state in the absence

and presence of drug, respectively, and k_{uptake}[°] and k_{uptake}^{*} are the rate constants for norepinephrine reuptake in the absence and the presence of drug, respectively.

In the presence of a drug which affects the norepinephrine reuptake site, the rate constant for norepinephrine reuptake, k_{uptake}^{*}, can be expressed by the following equation:

$$k_{\text{uptake}}^{*} = \frac{V_{\text{max}}}{Kd(1 + Cd/Kn)} = \frac{k_{\text{uptake}}^{\circ}}{1 + Cd/Kn} \quad (4)$$

The ratio of C_s^{*} to C_s[°] can be described as follows, by combining Equations 2 and 3.

$$\frac{C_s^{*}}{C_s^{\circ}} = \frac{k_{\text{uptake}}^{\circ}}{k_{\text{uptake}}^{*}} \quad (5)$$

Substitution of Equation 4 into Equation 5 gives Equation 6.

$$\frac{C_s^{*}}{C_s^{\circ}} = 1 + \frac{Cd}{Kn} \quad (6)$$

Quantitative prediction of the occurrence of piloerection from the change in α₁-adrenoceptor occupancy by endogenous norepinephrine

The α₁-adrenoceptor occupancy by endogenous norepinephrine in the absence of a drug (Φ[°]) can be expressed by Equation 7:

$$\Phi^{\circ} = \frac{C_s^{\circ}}{Ke + C_s^{\circ}} \quad (7)$$

where Ke represents the dissociation constant of norepinephrine for α₁-adrenoceptor (nM).

Moreover, the α₁-adrenoceptor occupancy by endogenous norepinephrine (Φ^{*}) in the presence of the drug is expressed by Equation 8.

$$\Phi^{*} = \frac{C_s^{*}}{Ke(1 + Cd/Kd) + C_s^{*}} \quad (8)$$

where Kd represents the dissociation constant of the drug for α₁-adrenoceptor.

The concentration of endogenous norepinephrine is assumed to be far lower than Ke as the concentration of endogenous norepinephrine and Ke have been reported to be 1.76 nM [19] and several micromolar [20], respectively, therefore Equations 7 and 8 can be rewritten as follows:

$$\Phi^{\circ} = \frac{C_s^{\circ}}{Ke} \quad (9)$$

$$\Phi^{*} = \frac{C_s^{*}}{Ke(1 + Cd/Kd)} \quad (10)$$

The ratio of Φ^{*} to Φ[°] can be written as follows:

$$\frac{\Phi^*}{\Phi^0} = \frac{C_s^*}{C_s^0} \left/ \left(1 + \frac{Cd}{Kd} \right) \right. \quad (11)$$

Then, substituting Equation 6 into Equation 11 in place of C_s^*/C_s^0 gives Equation 12.

$$\frac{\Phi^*}{\Phi^0} = \left(1 + \frac{Cd}{Kn} \right) \left/ \left(1 + \frac{Cd}{Kd} \right) \right. \quad (12)$$

To predict the frequency of the piloerection occurrence for each drug, $A = 1 + \frac{Cd}{Kn}$, $B = 1 + \frac{Cd}{Kd}$ and Φ^*/Φ^0 were calculated using the parameters listed in Table 1. The calculated values of A, B and Φ^*/Φ^0 for each drug are listed in Table 2.

In the case of imipramine, its active metabolite, desipramine, also binds to the receptors in a competitive manner. Taking desipramine into consideration, Φ^*/Φ^0 can be expressed by the following Equation 12':

$$\frac{\Phi^*}{\Phi^0} = \left(1 + \frac{Cd}{Kn} + \frac{Cd'}{Kn'} \right) \left/ \left(1 + \frac{Cd}{Kd} + \frac{Cd'}{Kd'} \right) \right. \quad (12')$$

where C_d' and K_d' represent desipramine concentration and its dissociation constant for α_1 -adrenoceptor, respectively.

To predict the frequency of the piloerection occurrence for imipramine, $A = 1 + \frac{Cd}{Kn} + \frac{Cd'}{Kn'}$, $B = 1 + \frac{Cd}{Kd} + \frac{Cd'}{Kd'}$ and Φ^*/Φ^0 were calculated using the parameters listed in Table 1. The calculated values of A, B and Φ^*/Φ^0 for imipramine are listed in Table 2.

The present model assumes that the number of α_1 -adrenoceptors and its sensitivity are constant throughout; it should be noted that if receptor desensitization occurs, the severity of the symptom might be reduced.

In the present analysis, the Φ^*/Φ^0 value of milnacipran was compared with those of the other two antide-

pressants, fluvoxamine and imipramine. The greater the value of Φ^*/Φ^0 becomes, the greater the occurrence of piloerection.

Results

Changes in α_1 -adrenoceptor occupancy by endogenous norepinephrine (Φ^/Φ^0) by milnacipran, fluvoxamine and imipramine*

The changes in α_1 -adrenoceptor occupancy by endogenous norepinephrine following 25 mg p.o. administration of milnacipran, fluvoxamine and imipramine were calculated (Table 2). The values of A, which reflects the inhibitory potency of norepinephrine reuptake into nerve terminals, differed greatly among the drugs (the values for milnacipran, imipramine and fluvoxamine were 7.13, 4.63 and 1.01, respectively). The value of B, which reflects the inhibitory potency for α_1 -adrenoceptor, was 1.08 for imipramine, while those for milnacipran and fluvoxamine were 1.00–1.02 and 1.01, respectively. The Φ^*/Φ^0 values (A is divided by B) were 7.00–7.13 for milnacipran and 4.12 for imipramine. The receptor occupancy was not affected by fluvoxamine, i.e. the Φ^*/Φ^0 value was 1.00.

Milnacipran dose-dependent increase of α_1 -adrenoceptor occupancy by endogenous norepinephrine

The dosage dependency of milnacipran and fluvoxamine on the increase in Φ^*/Φ^0 values was analysed using the pharmacokinetic/pharmacodynamic (PK/PD) model (Figure 1). After oral administration of 12.5, 25, 50 and 100 mg milnacipran, the Φ^*/Φ^0 values were calculated to be 4.31, 7.00, 13.7 and 25.7, respectively. In contrast, after oral administration of 25, 50 and 100 mg fluvox-

Table 2

Change of α_1 -adrenoceptor occupancy following 25 mg p.o. administration of milnacipran, fluvoxamine and imipramine

Drug	A	B	$\Phi^*/\Phi^0 (= A/B)$
Milnacipran	7.13	>1.00, 1.02	>7.00, 7.13
Fluvoxamine	1.01	1.01	1.00
Imipramine	4.63	1.08	4.12

$$A = 1 + \frac{Cd}{Kn}; B = 1 + \frac{Cd}{Kd}; \Phi^*/\Phi^0 = A/B.$$

Figure 1

Dose-dependent increase of α_1 -adrenoceptor occupancy of endogenous norepinephrine (Φ^*/Φ^0) following oral administration of milnacipran. ● and □ indicate milnacipran and fluvoxamine, respectively

amine, the Φ^*/Φ^0 values were calculated to be 0.999, 0.997 and 0.994, respectively.

Discussion

This is the first report of piloerection associated with the use of milnacipran. Moreover, we have quantitatively estimated the increasing effect of milnacipran on the α_1 -adrenoceptor occupancy by endogenous norepinephrine, which is a possible index based on the putative mechanism of piloerection, by using PK/PD model analysis. The potency of milnacipran to induce increased α_1 -adrenoceptor occupancy of endogenous norepinephrine was stronger than those of the other antidepressants (fluvoxamine, imipramine and its metabolite, desipramine), and was dose dependent. These results suggest that milnacipran-induced piloerection is attributable to the activation of α_1 -adrenoceptor.

The ratio of α_1 -adrenoceptor occupancy by endogenous norepinephrine after administration of antidepressant to that without drug (Φ^*/Φ^0), which represents the occurrence of piloerection, can be calculated from the drug concentration in the synaptic cleft (C_d), the inhibitory constant for norepinephrine reuptake of the drug (Kn) and the dissociation constant of the drug for α_1 -adrenoceptor (Kd). The model analysis suggests that milnacipran increases the α_1 -adrenoceptor occupancy by endogenous norepinephrine via inhibition of norepinephrine reuptake ($A = 7.13$), while milnacipran itself barely inhibits α_1 -adrenoceptor ($1.00 < B < 1.02$) after single administration of 25 mg milnacipran (Table 2). Interestingly, the present analysis has also shown that the value of Φ^*/Φ^0 increased in proportion to the dose of milnacipran from 12.5 to 100 mg (Figure 1). This is possibly because the concentration of milnacipran in the synaptic cleft is higher than the Kn value, but far lower than the Kd value (Table 1). These findings strongly support that piloerection in the present case had been induced by milnacipran, and that the frequency of piloerection occurrence by milnacipran is dose dependent.

In the present case, piloerection was not observed when the patient was receiving fluvoxamine. This phenomenon can be also explained by the fact that the Φ^*/Φ^0 value was estimated to be unchanged after administration of 25–100 mg of fluvoxamine (Table 2, Figure 1). This is because both the Kn and Kd values of fluvoxamine are much higher than the concentration of fluvoxamine in the synaptic cleft. Therefore, fluvoxamine is thought to have a low occurrence of inducing piloerection even at high dose.

In this analysis, the potencies of fluvoxamine and milnacipran to induce piloerection were estimated comparatively by using the present model, based on their

affinities for α_1 -adrenoceptor and the putative concentrations of the drugs. Although the analysis is not based on the individual pharmacokinetic data of the patient, the predicted ratio (Φ^*/Φ^0) was consistent with the observation that piloerection was induced by milnacipran, but not by fluvoxamine in this case. With respect to α_1 -adrenoceptor stimulation, fluvoxamine has characteristics distinct from milnacipran.

In the present case, piloerection was induced just after the replacement of fluvoxamine with milnacipran. Abrupt discontinuation of fluvoxamine may lead to a transitory serotonin deficiency, causing withdrawal symptoms [21]. However, piloerection is not a typical symptom of serotonin deficiency, and no reports suggest that the frequency of piloerection occurrence is affected by serotonin level. Therefore, it is unlikely that piloerection is caused by the discontinuation of fluvoxamine.

In the present case, tizanidine was used before and after the replacement of fluvoxamine with milnacipran. Tizanidine is a α_2 -adrenoceptor agonist and also behaves as a partial agonist of the α_1 -adrenoceptor at high concentration (1–100 μM) [22]. However, the maximum free plasma concentration of tizanidine is estimated to be about $5 \times 10^{-3} \mu\text{M}$ [23], so α_1 -adrenoceptor stimulation by tizanidine appears unlikely to be clinically significant. It remains unknown whether tizanidine may modulate the extent of drug-induced piloerection via an α_2 -adrenergic effect.

The α_1 -adrenoceptor-mediated side-effects of milnacipran other than piloerection may also be predicted by the Φ^*/Φ^0 value. For example, urinary bladder smooth muscle is regulated by both adrenergic and anticholinergic nerves [24]. As milnacipran does not substantially bind to mACh receptor [25], milnacipran-induced dysuria is conceivably mediated by α_1 -adrenoceptor but not by anticholinergic action. Indeed, milnacipran has a seven-fold higher frequency of dysuria than fluvoxamine [26], being consistent with the Φ^*/Φ^0 values of milnacipran and fluvoxamine. Tachycardia and hypertension may also be induced by α_1 -adrenoceptor activation. Indeed, a high dose of milnacipran (150 mg day^{-1}) is reported to induce hypertension [27]. Our model may be useful for prediction of dysuria and hypertension by antidepressants, as well as piloerection.

The present case is the first to report piloerection induced by milnacipran and the frequency of this side-effect is still unknown. Since piloerection is a common physiological symptom, it may not be regarded as a drug-induced reaction even by medical staff. Moreover, the symptom of drug-induced piloerection is sometimes described as paraesthesia or chills, as was reported in the case of midodrine, an α_1 -adrenoceptor agonist [28].

We cannot rule out the possibility that the plasma concentration of milnacipran or the sensitivity of α_1 -adrenoceptors was greater than average in this patient.

Venlafaxine, another SNRI, is also widely used. The maximum plasma unbound concentration of venlafaxine after oral administration of 50 mg is 178 nM and far lower than its K_n value, 1260 nM [17]. It was also shown that venlafaxine did not inhibit α_1 -adrenoceptor. Therefore, the occurrence of α_1 -adrenoceptor-mediated adverse effects of venlafaxine is considered to be less frequent than that of milnacipran. Indeed, dysuria, piloerection and hypertension are uncommon for venlafaxine.

In the case of tricyclic antidepressants, the potency to increase α_1 -adrenoceptor occupancy via norepinephrine reuptake inhibition is expected to be attenuated by their well-known antagonistic action towards α_1 -adrenoceptor. Indeed, the inhibitory potencies of tricyclic antidepressants for α_1 -adrenoceptor are higher than those of milnacipran and fluvoxamine, as assessed by comparing the K_d values. However, the present model predicted that imipramine may cause piloerection by increasing the α_1 -adrenoceptor occupancy by endogenous norepinephrine, because the putative concentrations of imipramine and desipramine are lower than the K_d values and the concentration of desipramine is higher than the K_n value. Indeed, piloerection has been reported in a clinical trial of imipramine [29]. These facts strongly imply that it is important for the quantitative prediction of α_1 -adrenoceptor-mediated adverse reactions to take into account the potencies of both norepinephrine reuptake inhibition and blockade by using the present PK/PD model.

The patient stated that piloerection had gradually abated within a week after the start of milnacipran, and no further piloerection occurred even with a higher dose of the drug. Piloerection is caused by the stimulation of α_1 -adrenoceptors, which are subsequently prone to be desensitized [30, 31]. Indeed, in the case of midodrine, an α_1 -adrenoceptor agonist, piloerection occurs as a transient and dose-dependent phenomenon [28]. We did not model the disappearance of piloerection in the present case, because we did not have precise data on the time course of the extent or occurrence of the patient's piloerection. A model incorporating the desensitization of α_1 -adrenoceptors may be needed to analyse the disappearance of α_1 -agonist-induced piloerection. The discontinuation of fluvoxamine is not likely to have been involved in the amelioration of piloerection, since the half-life of fluvoxamine is about 10 h [12], which is far shorter than the time scale of the decrease in piloerection.

In conclusion, we present the first case of milnacipran-induced piloerection. The model analysis is consistent with the view that milnacipran induces α_1 -adrenoceptor-agonistic side-effects, such as piloerection, via norepinephrine reuptake inhibition. In the present analysis, we evaluated the frequency of drug-induced piloerection, focusing on antidepressants which have both α_1 -adrenoceptor stimulating and inhibitory effects. Although α_1 -adrenoceptor-antagonistic effects have thus far been considered mainly as adverse effects of antidepressants, potential α_1 -adrenoceptor-agonistic events should also be considered, not only for milnacipran, but also for other antidepressants that inhibit norepinephrine reuptake.

Competing interests: None declared.

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