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ASUNTO	Radicación	09-149219	2.15165
	Trámite	011	
	Evento	379	
	Actuación	519	
	Oficio		
	Folios	006	

Patente de Invención ☒

Vía Nacional ☐

Vía PCT (Fase Nacional) ☒

Patente de Modelo de Utilidad ☐

Cap. I ☐

Cap. II ☒

No. Solicitud Internacional PCT/MX2008/000085

Fecha de Presentación Internacional 04 Julio de 2008

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 6 a 47	30/Diciembre/2009
Reivindicaciones:	Folios 48 a 50	30/Diciembre/2009
	Folios 156 a 158	12/Septiembre/2011
Oposiciones:	Folios 95 a 109	Lafrancol 25/Junio/2003
Respuesta del solicitante:	Folios 113 a 155	12/Septiembre/2011
Prioridad:	MX/a/2007/008321	06/Julio/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Composición farmacéutica que comprende la combinación de una triazolobenzodiazepina y un agente inhibidor selectivo de la recaptura de serotonina".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar compuestos útiles para el tratamiento y control de episodios depresivos mayores, síntomas del trastorno Obsesivo-Compulsivo (TOC), trastornos del pánico con o sin agorafobia, trastornos de ansiedad generalizada, fobia social y desorden de estrés postraumático.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica compuesta por una combinación sinérgica de un agente inhibidor selectivo de la recaptación de serotonina y un agente perteneciente al grupo de las triazolobenzodiazepina.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 31/5517

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es clara, ya que si bien no esta encabezada por un uso hace referencia al uso que se puede dar a la invención.

La reivindicaciones 1, 2,3 no son claras ya que describen un rango de dosis muy amplio de cada uno de los principios activos presentes en la composición farmacéutica. Se sugiere restringir dichos rangos de acuerdo con lo que se encuentra sustentado en el capítulo descriptivo.

Se requiere al solicitante hacer las aclaraciones necesarias.

5. Análisis de las Oposiciones

Argumentaciones de Lafrancol

Argumenta el doctor Tito Noé Parra Murillo en calidad de apoderado de la sociedad LAFRANCOL S.A, que la presenta solicitud no cumple con los requisitos de patentabilidad, novedad, nivel inventivo, aplicación industrial.

Las composiciones y combinaciones farmacéuticas donde se involucran agentes tales como Paroxetina y Alprazolam, es imprescindible manifestar que no puede la solicitante pretender acceder a un beneficio patentario sobre composiciones y combinaciones farmacéuticas que comprenden moléculas que se encuentran descubiertas y plenamente identificadas en el sector químico farmacéutico. En los documentos anexos se encuentra "The Index Merck" puede observarse que es principio activo Paroxetina se encuentra bajo conocimiento publico y ostenta beneficios patentarios concedidos por Alemania DE 2404113, la Oficina Europea de Patentes EP 223403 y Estados Unidos De América US 3912743, US 4007196, US 4721723. De igual manera, Alprazolam ostenta beneficios patentarios concedidos por Alemania DE 2012190 y Estados Unidos de América US 3987052. No puede existir beneficio patentario que reivindique composiciones y combinaciones farmacéuticas útiles en el tratamiento y/o prevención de la depresión o del síndrome de abstinencia,

que resultan carentes de novedad y nivel inventivo, ya que como es evidente, son eventos conocidos mundialmente. La mezcla (combinaciones) de productos (moléculas) conocidos y su variación, bien sea en uso, forma, dimensión o materia, no se consideran invenciones por cuanto no son susceptibles de aplicación industrial, nivel inventivo y novedad.

Respuestas del Solicitante

En relación con los fundamentos de la oposición formulada a nombre de la sociedad LAFRANCOL S.A. se señala que el opositor no aporta ningún documento o prueba que evidencia la falta de novedad o actividad inventiva de la invención. Debido que en los documentos anexos no muestran la combinación específica que se reclama en la presente invención, por lo cual no puede verse afectada la novedad de la misma. Las reivindicaciones precisan novedad y altura inventiva de los productos que se busca proteger con la patente ya que ninguna versa sobre los principios activos Paroxetina o Alprazolam en forma aislada. La presente invención consiste en la combinación sinérgica de un agente inhibidor de la recaptación de serotonina como Paroxetina y de un agente del grupo de las triazolobenzodiazepina, tal como el Alprazolam.

Con el fin de proporcionar pruebas adicionales que demuestren efecto sinérgico se anexan los resultados del estudio pre clínico titulado "Interacción sinérgica de la combinación de Paroxetina y Alprazolam por vía oral en la rata en el modelo experimental de depresión (nado forzado) y en el modelo experimental de ansiedad (laberinto elevado en cruz)".

De acuerdo a los resultados obtenidos se tiene que en la prueba de nado forzado administrando la combinación Paroxetina-Alprazolam presento un efecto sinérgico en la potenciación del efecto antidepresivo disminuyendo el porcentaje de tiempo de inmovilidad en la prueba de nado forzado. En la prueba de laberinto elevado en cruz, la combinación de Paroxetina – Alprazolam presenta sinergia, potenciando el efecto ansiolítico, incrementando el porcentaje de tiempo en áreas abiertas en relación al presentado con la administración del Alprazolam en forma individual. El análisis isobolográfico de la combinación Paroxetina-Alprazolam demostró efecto sinérgico de potenciación en cada uno de los modelos evaluados.

Por lo anterior se concluye que la combinación Paroxetina + Alprazolam es sinérgica y evidencia que la combinación mejora lo conocido en el estado de la técnica dando lugar a un producto nuevo, por lo que cumple con el requisito de novedad. Se concluye que la sinergia existente entre Paroxetina y Alprazolam se alcanzo luego de analizar e investiga, después de una etapa inventiva, por lo tanto, cumple con el requisito de nivel inventivo.

Respuesta del Examinador Técnico

Ante la oposición interpuesta por el doctor Tito Noé Parra Murillo en calidad de apoderado de la sociedad LAFRANCOL S.A. y de acuerdo a los documentos anexos, los cuales corresponden a "The Index Merck" puede observarse que el principio activo Paroxetina se encuentra bajo conocimiento publico y ostenta beneficios

patentarios concedidos por Alemania DE 2404113, la Oficina Europea de Patentes EP 223403 y Estados Unidos De América US 3912743, US 4007196, US 4721723. De igual manera, Alprazolam ostenta beneficios patentarios concedidos por Alemania DE 2012190 y Estados Unidos de América US 3987052. Dichos documentos no divulgan o sugieren la combinación de los principios activos de la presente solicitud en una composición farmacéutica, por lo tanto no desvirtúan la patentabilidad de esta solicitud y no serán tenidos en cuenta en el examen de patentabilidad.

De acuerdo con la respuesta de la Doctora Dilia María Rodríguez D'aleman en calidad de apoderado de la sociedad WORLD-TRADE IMPORT-EXPORT, WTIE,AG. y los documentos anexos, estos evidencian un efecto sinérgico de la combinación de Paroxetina – Alprazolam, respecto al efecto presentado por los principios activos administrados en forma independiente, evaluados en la prueba de nado forzado para Paroxetina y en la prueba de tiempo en las áreas abiertas del laberinto en cruz para el Alprazolam. Teniendo en cuenta que la combinación Paroxetina - Alprazolam presenta efecto sinérgico, de acuerdo a lo anterior, vale la pena aclarar, que dicha combinación, en los intervalos de dosis para administración reivindicados en la presente solicitud, son conocidos en el estado de la técnica, en donde se realizó un estudio en personas adultas sanas. De igual manera, el estado de la técnica revela que la administración combinada de Paroxetina y Alprazolam presento efectos adversos en adultos mayores, tal como se describe en el examen de patentabilidad.

6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: Julio 06 de 2007, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	Lack of pharmaceutical interaction between Paroxetine and Alprazolam at steady in healthy volunteers.	Journal of Clinical Psychopharmacology. Volumen (3) Págs 268-76.	Junio/2004

D1 <http://www.ncbi.nlm.nih.gov/pubmed?term=Lack%20of%20pharmacologic%20interaction%20between%20paroxetine%20and%20alprazolam%20at%20steady%20state%20in%20healthy%20volunteers>.

Divulga (Abstract) un estudio de terapia combinada de Paroxetina y Alprazolam.

7. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una composición farmacéutica compuesta por la combinación sinérgica de un agente inhibidor selectivo de la recaptación de serotonina y un agente perteneciente al grupo de las triazolobenzodiazepina, caracterizada porque el agente inhibidor selectivo de la recaptación de serotonina es el principio activo: Paroxetina hemidrato del Clorhidrato de Paroxetina y el agente

perteneciente al grupo de las triazolobenzodiazepina es el principio activo Alprazolam, así como excipientes farmacéuticamente aceptables; en donde dichos principios activos se encuentran presentes en la formulación en un rango de concentración de 20 mg hasta 40 mg para la Paroxetina hemidrato del clorhidrato de Paroxetina y de 0.25 mg hasta 4 mg para el Alprazolam; los cuales se encuentran formulados en una sola unidad de dosificación para ser administrada por vía oral, misma que esta indicada para el control y tratamiento de episodios depresivos mayores, síntomas del trastorno Obsesivo-Compulsivo (TOC), trastornos del pánico con o sin agorafobia, trastornos de ansiedad generalizada, fobia social y desorden de estrés postraumático. (Fl. 156 – 157)

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
Composición farmacéutica que comprende un inhibidor selectivo de recaptación de serotonina, Paroxetina 20mg – 40 mg	Combinación de Paroxetina 20 mg/d
Y un agente perteneciente al grupo de triazolobenzodiazepina, Alparazolam 0.25mg – 4mg	Y Alprazolam 1mg/d

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en el documento D1, el cual da a conocer un estudio en donde se evaluo la administración combinada de los principios activos Paroxetina y Alprazolam en dosis de 20 mg/d y 1mg/d respectivamente en las dosis descritas una vez al día, durante 15 días. El estudio se realizo en 25 voluntarios, adultos jóvenes sanos los cuales se les administro 4 secuencias de tratamiento las cuales corresponden a Paroxetina-Alprazolam placebo, Alprazolam-Paroxetina placebo, Paroxetina-Alprazolam y Paroxetina placebo – Alprazolam placebo en orden aleatorio. Esto con el fin de evaluar la interacción farmacocinética de la terapia combinada y se observo que no se producía interacción entre los principios activos. (Fl. 159). Adicionalmente, es conocido en el estado de la técnica, en un estudio en el cual se evaluó los efectos adversos provocados con la administración simultánea de inhibidores de la recaptación de serotonina y anti psicóticos. En donde se administraron diariamente de forma conjunta, Paroxetina (20mg) y Alprazolam (1.2mg), en el tratamiento de la depresión y de la ansiedad en donde se evidenció la producción del síndrome maligno neuroléptico como una complicación en el tratamiento anti psicótico⁽¹⁾. (Fl.160 - 163).

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 2 – 4 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

1 Tanii H, Ichihashi K, Inoue K, Fujita K, Okazaki Y. " Possible neuroleptic syndrome related to cncomitant treatment with Paroxetine and Alprazolam". Vol 30, Págs. 1176 – 1178.
Expediente 09 149 219 1er Art 45

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	Lack of pharmaceutical interaction between Paroxetine and Alprazolam at steady in healthy volunteers.	1 – 4	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
28 AGO. 2012

Elaborado por: Paola Duarte *Paola*
Revisado por: Consuelo Leguizamón Leguizamón *CL*
Aprobado por: José Luis Salazar López

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Lack of pharmacologic interaction between paroxetine and alprazolam at steady state in healthy volunteers.

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Abstract

This investigation aimed to provide evidence on the lack of pharmacokinetic interaction of paroxetine (20 mg/d) and alprazolam (1 mg/d) in combined therapy. In addition, the central effects of both drugs when administered alone and in combination were assessed to rule out any relevant synergistic depressant central effect. Twenty-five healthy young adult volunteers participated in a double-blind, double-dummy, placebo-controlled, repeated dose (15 days), 4-period crossover study. Each subject received each of 4 treatment sequences (ie, paroxetine-alprazolam placebo, alprazolam-paroxetine placebo, paroxetine-alprazolam, and paroxetine placebo-alprazolam placebo) in randomized order. The ratios for area under the curve within a dosing interval and maximum plasma concentration of the paroxetine plus alprazolam sequence to single agent paroxetine were 1.07 (90% confidence interval = 0.99 to 1.16) and 1.05 (90% confidence interval = 0.97 to 1.13), respectively, with no statistically significant differences between the 2 treatments. Similarly, for alprazolam, ratios for the combined to the single treatment sequence were 0.99 (90% confidence interval = 0.93 to 1.05) and 1.00 (90% confidence interval = 0.94 to 1.07) for area under the curve within a dosing interval and maximum plasma concentration, respectively, showing no evidence for interaction. Comparative pharmacodynamics on the combination was assessed using 6 Psychomotor Performance Tests and 5 Visual Analogue Scales focused on mood variables. Alprazolam and paroxetine plus alprazolam induced similar and significant performance impairment and sedation after both single and repeated dose administration, being less evident on day 15. After dosing, paroxetine plus alprazolam showed a lower recovery pattern than alprazolam alone, especially on day 15. No treatment sequence showed cumulative effects after repeated dose administration. Psychomotor Performance Tests and Visual Analogue Scales data suggested lack of pharmacodynamic interactions. Accordingly, study results showed no evidence for pharmacologic interactions between paroxetine and alprazolam at steady state. The most commonly reported adverse event was drowsiness, with a higher incidence under both single and combined alprazolam treatments.

PMID: 15116480 [PubMed - indexed for MEDLINE]

Case report

Possible neuroleptic malignant syndrome related to concomitant treatment with paroxetine and alprazolam

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Abstract

A 74-year-old man with depressive symptoms was admitted to a psychiatric hospital due to insomnia, loss of appetite, exhaustion, and agitation. Medical treatment was initiated at a daily dose of 20 mg paroxetine and 1.2 mg alprazolam. On the 10th day of paroxetine and alprazolam treatment, the patient exhibited marked psychomotor retardation, disorientation, and severe muscle rigidity with tremors. The patient had a fever (38.2 °C), fluctuating blood pressure (between 165/90 and 130/70 mm Hg), and severe extrapyramidal symptoms. Laboratory tests showed an elevation of creatine phosphokinase (2218 IU/L), aspartate aminotransferase (134 IU/L), alanine aminotransferase (78 IU/L), and BUN (27.9 mg/dl) levels. The patient received bromocriptine and diazepam to treat his symptoms. 7 days later, the fever disappeared and the patient's serum CPK levels were normalized (175 IU/L). This patient presented with symptoms of neuroleptic malignant syndrome (NMS), thus demonstrating that NMS-like symptoms can occur after combined paroxetine and alprazolam treatment. The adverse drug reaction score obtained by the Naranjo algorithm was 6 in our case, indicating a probable relationship between the patient's NMS-like adverse symptoms and the combined treatment used in this case. The involvement of physiologic and environmental aspects specific to this patient was suspected. Several risk factors for NMS should be noted in elderly depressive patients whose symptoms often include dehydration, agitation, malnutrition, and exhaustion. Careful therapeutic intervention is necessary in cases involving elderly patients who suffer from depression.

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Keywords: Alprazolam; Depression; Neuroleptic malignant syndrome; Paroxetine

1. Introduction

Since neuroleptic malignant syndrome (NMS) is a life-threatening complication of antipsychotic treatment that can cause significant adverse side effects, the prevention of NMS is an important issue in the field of clinical psychiatry. NMS is characterized by severe muscle rigidity, hyperthermia, diaphoresis, dysphagia, incontinence, changes in the level of consciousness, and elevated serum creatine phosphokinase (CPK) (American Psychiatric Association, 1994). Virtually all neuroleptics are capable of inducing NMS, including the newer atypical antipsychotics and antidepressant agents. In addition to the anti-dopaminergic activity of neuroleptics (Hashimoto et al., 1984; Henderson and Wooten, 1981), serotonergic activation as well as GABAergic deficiency has

been suggested as possibly being involved in the pathogenesis of NMS (Ebari et al., 1990; Lew and Tollefson, 1983). NMS has also been reported during the treatment of depression with tricyclic antidepressants (TCAs) (Langlow and Alarcon, 1989; Taylor and Schwartz, 1988). Though rare, NMS can also be an adverse reaction induced by serotonin re-uptake inhibitors such as paroxetine or fluoxetine in cases when there is concomitant treatment with antipsychotics (Kontaxakis et al., 2003a,b). In this report, we present the case of an elderly male suffering from depression and anxiety who developed NMS while being treated simultaneously with paroxetine and alprazolam. To the best of our knowledge, this is the first case report of NMS related to concomitant alprazolam treatment.

2. Case report

A 74-year-old man had been a healthy farmer before beginning to experience depression with anxiety after taking on a number of

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new social roles (e.g., leader of an association for the elderly and chairman of a funeral home, participating in the restoration of a temple, etc.). The patient did not have any past history of substance abuse, previous drug exposure or comorbid psychiatric diagnoses. The patient was admitted to a psychiatric hospital due to depressed mood, insomnia, loss of appetite, exhaustion, and agitation. His psychiatric symptoms had been continued for more than 3 weeks. The patient was diagnosed as having major depression according to the DSM-IV criteria. An initial daily dose of 20 mg paroxetine and 1.2 mg alprazolam was administered to the patient. On the 10th day of paroxetine and alprazolam treatment, the patient exhibited marked psychomotor retardation, disorientation, and severe muscle rigidity with tremors. In addition, the patient had a fever (38.2 °C), fluctuating blood pressure (between 165/90 and 130/70 mm Hg, normally ca 125/65), elevated pulse (96/min), and severe extrapyramidal symptoms. Laboratory tests showed elevations in the levels of creatine phosphokinase (CPK) (2218 IU/L), aspartate aminotransferase (134 IU/L), alanine aminotransferase (78 IU/L), and blood urea nitrogen (27.9 mg/ml). A slightly elevated WBC ($9.8 \times 10^9/L$) was also observed. However, the patient's creatinine, electrolyte, blood sugar, and C-reactive protein levels, as well as the cerebrospinal fluid data were all within normal limits. The serological assays for HSV were negative. A computerized tomography scan of the brain did not reveal any remarkable abnormalities, except for mild brain atrophy; the possibility of infectious disease was excluded. Paroxetine and alprazolam were discontinued, and the patient received bromocriptine and diazepam treatment. Bromocriptine (7.5 mg/day) and diazepam (4 mg/day) were administered to the patient for 6 days. Bromocriptine treatment was discontinued when the patient's primary symptoms disappeared. 7 days later, the patient's muscle rigidity had resolved and his serum CPK levels were normalized (175 IU/L). The patient was not re-challenged with either antidepressants or alprazolam after this episode, and treatment with 2 mg of diazepam was continued until the patient was discharged from the hospital. The patient slowly recovered and was discharged on the 64th day after the onset of NMS.

3. Discussion

The patient described here exhibited symptoms of neuroleptic malignant syndrome, including rigidity, fever, and autonomic instability; he met the DSM-IV criteria for neuroleptic malignant syndrome, with the exception of the use of neuroleptic medication, thus demonstrating that NMS-like symptoms can occur in association with paroxetine and alprazolam treatment. A Naranjo adverse drug reaction probability score of 6 suggested the combination of paroxetine and alprazolam as the probable cause of these changes (Naranjo et al., 1981). In the present case, it was also appropriate to consider serotonin syndrome (SS) in the differential diagnosis (Radomski et al., 2000). Here, it was difficult to rule out SS (Kontaxakis et al., 2003a), but this patient's symptoms were not typical of those of SS, because they did not include hyperreflexia and myoclonus (Rusyniak and Sprague (2005). It was difficult to rule out lethal catatonia (LC) in our case, a disorder which was also a relevant consideration in the differential diagnosis. Indeed, clinical features of LC and

NMS are often indistinguishable from each other (Carroll and Taylor, 1997; Van Den Eede et al., 2005). LC may develop in association with affective illness, and the possibility should be considered that the catatonia in this case was not induced by combined paroxetine and alprazolam treatment. However, the patient exhibited the above clinical state when he was treated with the two aforementioned drugs. It has also been reported that LC often requires neuroleptic treatment (Castillo et al., 1989), and does not respond to conventional NMS treatment with dantrolene and bromocriptine (Cassidy et al., 2001). The patient in the present case was successfully treated with bromocriptine and diazepam, which was thought to provide at least partial support for a diagnosis of NMS. It should be noted that NMS induced by concomitant treatment with paroxetine and an atypical antipsychotic agent has been reported in a previous study (Kontaxakis et al., 2003b). The putative mechanism of NMS due to paroxetine has been proposed to be the extrapyramidal side effects of a selective serotonin reuptake inhibitor and the inhibitory effects of elevated serotonin levels on dopamine activity (Tsai et al., 2003). To the best of our knowledge, the present case is the first to be reported of NMS-like symptoms associated with concomitant treatment with alprazolam in combination with paroxetine. Benzodiazepines, the most widely prescribed psychotropic drugs, are often used in patients with depressive disorders, either alone or in combination with standard antidepressants. Among the benzodiazepines, diazepam is known to have a therapeutic effect on patients with NMS (Kumar, 1987; Lew and Tollefson, 1983), and the development of NMS associated with a discontinuation of alprazolam has been described previously (Burch and Downs, 1987). These previous results suggest that a relative central dopaminergic and gamma-amino butyric (GABA) imbalance might be related to the onset of NMS, and treatment with diazepam appears to compensate for this imbalance. The inhibitory neurotransmitter GABA has extensive neural connections in the mesolimbic regions that appear to modulate dopamine. A second-messenger system constituent, inositol, may also be involved (Corradetti et al., 1987). Alprazolam, a high-potency benzodiazepine, has been reported to influence monoaminergic neurotransmitter systems such as the norepinephrine, dopamine, GABA, and serotonin systems (Santagostino et al., 1998). Alprazolam is a useful treatment option for certain patients who require rapid therapeutic effects and in whom standard antidepressant medications are contraindicated, poorly tolerated, or possibly ineffective. Alprazolam is metabolized by the cytochrome P450 subfamily (CYP3A). The doses of paroxetine and alprazolam commonly used are relatively low, and paroxetine is known to be a potent CYP2D6 inhibitor that exerts only a negligible effect upon the metabolism of alprazolam; thus, the induction of neuroleptic malignant syndrome might not be associated with an increase in the paroxetine and/or alprazolam concentration. On the other hand, it has also been reported that alprazolam is more toxic than other benzodiazepines due to the relative brevity of its half-life, thus indicating that co-ingestion of other medications such as TCAs could be expected to significantly worsen the outcome in patients on such a treatment regimen.

(Isbister et al., 2004). When alprazolam was used in an animal-model study to treat adult rats, a considerable increase in the density of both dopamine D1 and D2 receptors was observed in the striatum (Giardino et al., 1998); the results of that study suggested that alprazolam may affect dopamine receptors and lead to unusual adverse reactions. In the present case, the co-administration of alprazolam was not thought to be preventive, but it remains difficult to determine which of the two drugs would have been most responsible for facilitating the development of NMS in this patient concomitantly treated with paroxetine and alprazolam.

More importantly, the physiologic and environmental characteristics associated with this particular patient should be addressed in this context. NMS induced by antidepressants is at times observed in older adults with depression (Gupta and Racaniello, 2000; Washington et al., 1989). Risk factors for NMS include intramuscularly administered, abruptly increasing, high-dose neuroleptics; mental retardation; psychiatric symptoms (psychomotor agitation, catatonia, disorganization, and confusion); and certain physical conditions (dehydration and exhaustion). Several risk factors for NMS should be taken into account in cases involving elderly depressive patients whose symptoms often include dehydration, agitation, malnutrition, and exhaustion. Affective illness is another risk factor for neuroleptic malignant syndrome, and sympathetic nervous system activity is known to be increased in cases of major depression. The possibility remains that both age-related pharmacokinetics and certain pharmacodynamic changes may increase the clinical effects of these drugs in elderly patients. The reported findings suggest that both the direct effects as well as the indirect effects of paroxetine on extrapyramidal systems may interact with sympathetic nervous system dysfunction to produce the clinical features characteristic of neuroleptic malignant syndrome, which can be an adverse and even life-threatening side effect of such agents. Thus, careful therapeutic intervention is necessary in cases involving elderly patients who suffer from depression.

4. Conclusion

The present case shows that NMS can occur after concomitant treatment with paroxetine and alprazolam. The involvement of several risk factors for NMS should be noted in cases involving elderly depressive patients, as their symptoms often include dehydration, agitation, malnutrition, and exhaustion. Cautious therapeutic intervention should therefore be applied in elderly patients who suffer from depression.

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