I. Buj Álvarez
J. Pifarré Paredero
E. Idini
M. Puigdevall Ruestes

Repercussions of the withdrawal of thioridazine

Psychiatry Department
Hospital de Santa María
Lleida

Introduction. As a consequence of the withdrawal of thioridazine from the market, patients who have been treated with this drug require a new therapeutic approach. We have observed patients who require admission to acute unit due to decompensation resulting from the withdrawal of thioridazine who present a difficult management of therapeutic regime. The clinical characteristics and drug treatment needed to stabilize the patient are described.

Results. The sample obtained in our unit included 15 patients with a mean of 20 years of stability prior to withdrawal of thioridazine. This represents 6% of all the patients treated with thioridazine in 2005 in our health care area. They had a common psychopathological profile: affective pattern in addition to the psychotic symptomatology with predominance of emotional lability and hypomaniac tendency which is difficult to control pharmacologically. Clinical stabilization was obtained in 27% of patients by means of piperazine phenothiazines in monotherapy. An association with mood stabilizer and/or an atypical antipsychotic in 60% of patients was needed. In 40% we prescribed a mood stabilizer to manage affective instability and 27% responded to electroconvulsive therapy (ECT) treatment, which is indicated as a second option due to resistance to pharmacological treatment and/or presenting a serious condition.

Conclusions. We propose starting treatment with a group of piperazine phenothiazines, evaluating the introducing of mood stabilizers and/or ECT in each case. There have been 33% re-admissions, 40% of which required medium/long-term stay centers and one of which committed suicide. We demonstrate a high cost in terms of care, economic resources and of quality of life (autonomy, social skills and cognitive level) in our sample as a result of Meleril® (thioridazine) withdrawal of the market.

Key words:
Thioridazine. Meleril. Withdrawal. Schizophrenia. Typical antipsychotic.

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Correspondence:
Imma Buj Álvarez
Departamento Psiquiatría
Hospital de Santa María
Lleida (Spain)
E-mail: ibuj@gss.scs.es

Repercursiones de la retirada de la tioridazina

Introducción. Como consecuencia de la retirada del mercado de la tioridazina, pacientes que habían sido tratados con este fármaco requieren un nuevo abordaje terapéutico. Observamos casos de ingreso en unidad de agudos por descompensación tras la retirada de tioridazina y que presentan difícil manejo terapéutico. Se realiza una descripción de las características clínicas y de la pauta farmacológica que lleva a la estabilización del paciente.

Resultados. La muestra obtenida en nuestra unidad es de 15 pacientes con una media de 20 años de estabilidad previa a la retirada de tioridazina. Representan un 6% de todos los pacientes en tratamiento con tioridazina durante 2005 en nuestra región sanitaria. Presentaron un perfil psicopatológico común: patrón afectivo sobreañadido a la clínica psicótica, predominando labilidad emocional y tendencia a hipertimia de difícil manejo farmacológico. En un 27% se consiguió estabilidad con fenotiazinas piperazinas en monoterapia; en un 60% se requirieron la asociación con eutimizante y/o a antipsicótico atípico. Un 20% se estabilizaron con antipsicóticos atípicos en monoterapia. En un 40% pautamos eutimizante para manejar la inestabilidad afectiva y un 27% presentaron respuesta a tratamiento con terapia anticonvulsiva (TEC), que se prescribe de segunda elección debido a la resistencia al tratamiento farmacológico asociado a gravedad.

Conclusiones. Proponemos iniciar un tratamiento con el grupo de fenotiazinas piperazinas valorando la introducción de un eutimizante y/o TEC. Se ha producido un 33% de reingresos; un 40% de los casos han requerido centros de media/larga estancia y registramos un suicidio consumado. Observamos un elevado coste tanto de recursos asistenciales, económicos como de calidad de vida (autonomía, habilidades sociales y nivel cognitivo) en nuestra muestra tras la retirada de tioridazina.

Palabras clave:
Tioridazina. Meleril. Retirada. Esquizofrenia. Antipsicótico típico.

INTRODUCTION

Thioridazine belongs to the group of piperazine phenothiazines. It is included in the low potency or sedative group together with chlorpromazine and levomepromazine as it has anticholinergic, sedation and hypotension effects versus the high potency or incisive group. Thioridazine is characterized by having a less potent effect on the D2 nigrostriatal receptors and has an affinity for 5HT2. That is how the chlorpromazine levomepromazine low frequency of extrapyramidal effects, with high incidence of orthostatic hypotension pictures due to alpha-adrenergic blockade, is explained. Stressing the elevated affinity for the D2, D3, D4, α1, α2 and H5T2 receptor according to their profile, we could initiate the discussion on its atypicity within its category of typical antipsychotic drug. Thioridazine was authorized in 1959 in Spain as treatment of second choice in schizophrenia as principal indication.

Until restrictions were reported in 2001, its indications included anxiety, agitation and restlessness in the elderly, moderate-severe moderate psychomotor agitation, heteroaggressive and impulsive behavior disorders, mania/hypomania conditions and behavior disorders and epilepsy in children. During the period 1991-2000, this antipsychotic was the one used most in the UK with an average of 36% of the yearly antipsychotic prescriptions in that country. It must be stressed that the use of thioridazine during this period increased while the use of other typical ones (chlorpromazine, flupenthixol and trifluoperazine) decreased and the increase of atypical antipsychotics was initiated in the last years of the study[5]. We can venture to say at this point that there is a specific psychopathological profile that benefits from its receptorial profile[6,9]. According to the data sheet, the therapeutic doses are in the range of 200-600 mg/day.

The most frequent adverse effects were somnolence together with sedation as well as the anticholinergic effects. It caused sexual dysfunction, galactorrhea and weight increase in relationship to the increase of prolactin as there is imbalance of the tuberoinfundibular pathway. On the cardiovascular level, orthostatic hypotension was frequent and there could be moderate tachycardia, arrithymias and ECG alterations. The elevated dose, rapid increase of the dose and i.m. administration, especially i.v. (only the oral presentation was available in Spain) were factors that could be associated to the prolongation of the QRS or QT interval with risk of serious arrithymias, such as polymorphic ventricular tachycardia in Torsades de Pointes and ventricular fibrillation. Cases of irreversible pigmentation of the retina, followed by blindness with thioridazine dose greater than 800 mg/day have been described, with the diagnosis of pigmentary retinitis.

In 2001, the Spanish Health Care Products and Drug Agency (AEMPS) restricted the indications of Meleril® and modified the information contained in both the data sheet and in the leaflet due to the risk of QT prolongation, cardiac arrithymias and sudden death. In 2000, Reilly et al.[2,3] published a review on arrithymias and abnormalities in the QT in relationship to the administration of psychotropic drugs based on previously know evidence. In 2003, Whitchel and Hancox7 stressed the need to be cautious with the association of thioridazine-sudden death, arrhythmias, Torsades de Pointes since they suggested a multifactorial cause. It is very rare that an abnormal ventricle develops Torsades de Pointes. It is the concurrence of severe risk factors (hypokaliemia, bradycardia, gene HERG K+ gene block) that may reduce the reserve for correct cardiac repolarization. Thus, although there was low risk of cardiac complications, due to the evidence of the success of thioridazine as treatment, its global withdrawal was not justified. The authors suggested evaluation in each individual case. Data from some studies motivated that the FDA of the USA recommended changes in the drug authorization conditions given its arrhythmogenic potential since it could cause QTc prolongation. The recommendations of the FDA were very restrictive. The indication only remained in cases of schizophrenia that had not had an acceptable response to other antipsychotics. Those patients who are candidates should undergo a baseline ECG and their serum potassium should be measured. If the QT interval is > 450 msec, treatment with thioridazine should not be initiated. The potassium and ECG monitorings were regular. Treatment should be discontinued if the QTc is > 500 msec.

On 18/1/2005 the AEMPS communicated that the acceptance of the application to suspend the marketing of thioridazine made by Novartis Pharmaceuticals would be effective on June 30, 2005 based on the adverse effects and given the existence of other alternative treatments for Schizophrenia, the application to suspend it was accepted, this being done simultaneously in all of the European countries. Bisset et al.[4] indicated that there could be another reason for its withdrawal, the extremely low cost of the molecule compared with 2nd generation antipsychotic drugs. Lasser K et al. had already reported in 2002 that the new drugs have a high risk of side effects, which were not known until the post-marketing drug stage[8].

In our clinical practice, we conducted a collection of all the decompensation cases of the baseline disease with at least a 2 year background of psychopathological disease while under treatment with thioridazine that required admission to the Psychiatric Acute Unit of the Hospital of Santa María, reference unit for almost all the province of Lerida (a sector of approximately 360,000 inhabitants) from January 2006 to May 2007. We compiled the patients under treatment with thioridazine with doses greater than 50 mg/day in our health care region in the last year. The objectives were to study how many patients required admission for decompensation due to the withdrawal of thioridazine, calculate the percentage of relapses after its withdrawal, describe the psychopathological profile of these patients and indicate the most adequate pharmacological group or therapeutic association.

Our hypotheses are that patients who suffer decompensation and require hospitalization are going to have a common psychopathological profile characterized by an affective pattern added to the psychotic disease due to the atypical receptorial profile of thioridazine. These patients will have a difficulty for stabilization with second generation antipsychotics, requiring complex drug treatment due to the effect of discontinuation[1] of a molecule that had induced neurotransmitter balance in patients who had been under treatment with established success for years. Thus, we consider that they will need an association of different biological treatments (first and second generation antipsychotics, mood stabilizers and/or electroconvulsive therapy-ECT).

RESULTS

Based on the public health sector studied for the year 2005, we found that 244 patients were under treatment with thioridazine at antipsychotic doses (these were considered to be between 50-600 mg/d, eliminating those patients who were taking doses less than 50 mg/d). A profile was observed of patients under treatment with thioridazine who had been psychopathologically stabilized, who were independent for daily life activities and who had good adaptation to the setting[1].

In our department, 15 patients who required admission to the acute hospitalization unit due to decompensation of the baseline disease caused by the withdrawal of thioridazine were recorded. They represented 6% of the population under treatment. In regards to the diagnosis according to DSM-IV classification, we observed: schizoaffective disorder in 5 cases, delusional disorder in 2 cases, schizophrenia 7 cases; paranoid type 2, indifferentiated 3, residual 1, one case of paranoid schizophrenia in moderate mental retardation and one case of bipolar type 1 disorder.

The profile of patient who requires admission has common characteristics: a median of 20 years (range from 4 to 35 years) of stability without hospitalization, with maintenance dose of thioridazine (2 cases with 50 mg/d, 8 cases with 100 mg/d, 2 cases with 200 mg/d, 3 cases with 300 mg/d), good family, social and even work functionality prior to the drug withdrawal and worsening of the psychotic symptoms, presenting predominance of affective symptoms together with deterioration of all the areas with difficult drug management after suspension of thioridazine. There is a common psychopathological profile as an affective pattern added to the psychotic symptoms is seen in 9 out of the 15 cases. There is a predominance of emotional lability together with the tendency to have difficult-to-manage hyperthymia within a psychotic nucleus. There is a pure affective case (bipolar disorder I) and 5 cases of psychotic symptoms without affective symptoms (4 cases of paranoid schizophrenia and 1 case of delusional disorder). It is observed that the decompensations in this type of patient who had been stabilized over a long period of time with thioridazine require complex drug combinations.

In the patients studied, we observed that 27% achieved stability with drugs from the piperazine phenothiazine group (trifluoperazine and perphenazine) in monotherapy. A total of 20% were stabilized with atypical antipsychotics in monotherapy (risperidone and olanzapine). We observed that 53% required combination of a mood stabilizer and/or antipsychotics (within this group of combinations, 13% have required an association of typical plus atypical antipsychotics without mood stabilizer). We found it necessary to use a mood stabilizing drug (valproate vs lithium in a proportion of 4:2) in 40% of the patients due to the difficulty to manage the affective instability. Patients with 27% of the common psychopathological profile have a good response to treatment with electroconvulsive therapy (ECT), which is prescribed as second choice as there is resistance to drug treatment associated to seriousness.

Between 6 to 11 sessions with bilateral application are necessary. Finally, it should be stressed that 33% of the sample required more than 2 drugs in combination (not considering anxyolitics, hypnotics or antidepressants). It is important to consider that most of the cases were under monotherapy with thioridazine and stable for years. There is a readmission incidence in these patients of 33% with elevated cost of deterioration, quality of life of the patient and economics.

In a relationship to the strategies tested in outpatients prior to the first admission, we have observed that there is a tendency to introduce atypical antipsychotics as first choice in replacement of thioridazine: the majority being with quetiapine as it is recommended as a substitute, risperidone, amisulpride, ziprasidone and olanzapine. There are different changes between one and the other and combinations were also initiated due to the lack of response to monotherapy. A typical antipsychotic drug (perphenazine) was only initiated in two cases. In 50% of the cases that were initiated with atypical antipsychotic drug, there is change or it was association with a classical AP.

DISCUSSION

There is a need to use combinations of biological therapies (drug therapy, ECT) for stabilization. Closely linked to this finding is the fact that these patients respond to classical antipsychotics in association to mood stabilizers and/or second-generation antipsychotics.

It should be considered that the atypical antipsychotic drug used most in a naturalistic way is risperidone and that this, at high doses, it has a receptorial profile similar to the classical ones as it acts massively on D2. The finding that in the five cases that only have a psychotic symptoms, there is an adequate response to both atypical and typical antips-

ychotics without needing to associate ECT and/or mood stabilizers, stands out.

The proposal that we suggest according to the results obtained is to initiate treatment with a group of piperazine phenothiazines and to increase the performance of the dose by evaluating the need to introduce mood stabilizers to control the affective symptoms if they occur. It is also necessary to evaluate treatment with ECT if there is resistant and serious affective symptoms of the episode due to the good response observed with this technique. Prior to withdrawal of thioridazine, the patients were independent for the activities of their daily life together with good community adaptation and good social, family and even work performance. The current condition of these patients after the withdrawal of thioridazine is that they have required hospitalization and re-hospitalizations (33%) in an Acute Unit and have required different mental healthcare devices on discharge units such as day hospital, middle/long stay centers. At present, 40% of the cases have been admitted to subacute and/or middle/long stay centers due to poor evolution, existence of one case of suicide and 53% are under outpatient follow-up.

There is an elevated cost for care, economic and quality of life resources as well as deterioration on the cognitive, autonomy and social skills level in these patients. According to Bisset et al.[4] the evidence on risks and benefits of thioridazine should be reviewed and more humane action guidelines considered in the future due to the consequences for these patients[10,11].

We suggest the need to conduct a more extensive review, probably multicenter, with a larger sample of patients who have required hospitalization and who had problems in stabilization after the withdrawal of thioridazine and of the profile of patients who have considered their psychopathological stability as out-patients by replacing thioridazine with another antipsychotic drug.

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