Letter to the editor

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Choice of and decreasing of the dosage of risperidone in the treatment of schizophrenia. Global versus individual criteria

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The use of unnecessarily high doses of risperidone (RSP) is a common practice in some reference hospitals of the Valencian Community. Even though two studies[1,2] initially supported a standard dose of 6 mg/day, only a third one totally defended treating the different types of schizophrenia with high doses of RSP. Thus, this work published by Gutiérrez et al. in 1998[3] seems hypothetically to be the *alma mater* of our initial premise due to the unquestionable high scientific-social visibility of its authors, the high number of cases studied and due to the Spanish journal that published it, having greater repercussion than its namesakes written in English in view of the low historical Spanish production in international journals. Furthermore, they absolutely concluded that those patients treated with RSP doses above 9 milligrams/day were hospitalized for fewer days (25.3 days versus 32.1 days, than when the dose was less than 6 milligrams), and that RSP was well tolerated by at least 90.7%. However, they did not clarify what percentage of patients there was per interval, the range and mean age of each group, or the individual data of within-group response. These results clearly contrast when the international literature is analyzed. Thus, Nyeberg et al., in 1999[4], stated that a 6 mg/day dose would produce a mean occupancy of D2 dopaminergic receptors of 82%. This is sufficient to produce extrapyramidal symptoms (EPS). At the same time, they warned about the advisability of not exceeding 80% occupancy, corresponding to a 4 mg/day RSP dose. The EPS also worsens with age[5,6], increasing 30% per decade after 42 years of age[7]. Thus, considering that the Gutiérrez et al. samples ranged from 18-87 years, with a mean age of almost 34 years, the almost total absence of EPS is very difficult to agree on.

A possible methodological explanation for the exaggerated optimum dose reported by Gutiérrez et al. is provided by Nyberg et al., 1999[4]. He stresses that the standard dose obtained from the analysis of large groups of patients, as occurs in the Spanish work, is generally greater than that really effective for most of the patients when they are studied individually. Thus, using the same dose of RSP, very different levels of this and its metabolite in blood are found for each patient so that their therapeutic responses are also very different. Therefore, there does not seem to be a general dose that can be used to extrapolate the responses of each subject in question. If the global responses or a large number of cases are considered, the inevitable tendency is to increase the supposed effective dose required for each subject. On the contrary, when analyzed individually, it is observed that a high percentage respond favorably with doses much lower than 6 mg/day and with the subsequent absence of extrapyramidal symptoms[4,8-14]. Furthermore, it is admitted that a minimum dose of RSP in the brain is sufficient to induce an antipsychotic effect.

Finally, the presence of the pharmaceutical company Janssen in this work lead to a large component of suspicion, supporting, for example, Friedman and Richter[15], who, when reviewing studies having conflicts of interests found an enormous correlation with positive findings, as occurs in the case in questions ($p < 0.001$, equivalent to a confidence interval greater than 99.9%).

On the other hand, if we compare the cost between treatment with RSP (capacity to block the 5HT2 and D2 receptors) with the classical haloperidol (Hp) one (only the D2) we find an enormous difference between both products. (www.vademecum.medicom.es/producto_detalle.cfm).

While a daily dose of 5 mgs/day of HP would cost 1.65 euros/month, that of RSP (6 mgs/day) would be 140.77 euros/month and at least 72 euros more if we use the controversial dose proposed previously of 9 mgs/day.

However, the use of RSP can counteract the differences in cost if the responses are analyzed individually. Thus, a recent study[13], using relatively small doses of RSP (mean: 3.3 mg/day) and HP (2.9 mg/day), demonstrated similar results in the treatment of the first episode of schizophrenia, but with a smaller percentage of relapses. Furthermore, what is of great clinical important, there was less EPS (better *compliance* and quality of life, with fewer subsequent drop-

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outs) in the RSP treated group. This can be explained because, although RSP and HP are almost equivalent regarding D2 receptor occupancy[16,17], the predominance of 5HT2 blocking activity of RSP on the D2 (EPS sponsor) increases the EPS appearance threshold. However, when the RSP dose is from 4 to 8 mg/day, the protector effect per 5HT2 block disappears, D2 occupancy prevailing[4] and the differences between both products are indistinguishable[18-20].

Thus, using RSP in those cases that apparently require larger doses than those recommended of between 4-6 mg/day is questionable if it loses its protector effect against the appearance of EPS after that. This protocol should also be corrected downwards when dealing with patients over 40 years as this would also avoid the appearance of EPS even below those doses. The use of classical neuroleptics with little EPS activity such as perphenazine or HP would not imply a more toxic profile than RSP when they exceed 6 mg/day, adding an immeasurable savings. This savings would make it possible to increase, for example, the psycho-social resources that are almost always scarce but play a determining role in the prevention and prognosis of mental diseases.

REFERENCES

1. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995; 166:712-26.
2. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825-35.
3. Gutiérrez M, Gibert J, Bobes J, Herraiz ML, Fernández A. Risperidone in the treatment of acute exacerbation of schizophrenia symptoms. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1998; 26:83-9.
4. Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L. Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. Am J Psychiatry 1999;156:869-75.
5. Yasui-Furukori N, Mihara K, Takahata T, Suzuki A, Nakagami T, De Vries R, et al. Effects of various factors on steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone: lack of impact of MDR-1 genotypes. Br J Clin Pharmacol 2004; 57:569-75.
6. Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Muller-Arends A, Weber K, et al. Risperidone plasma levels, clinical response and side-effects. Eur Arch Psychiatry Clin Neurosci 2005; 255:261-8.
7. Aichhorn W, Weiss U, Marksteiner J, Kemmler G, Walch T, Zernig G, et al. Influence of age and gender on risperidone plasma concentrations. J Psychopharmacol 2005;19:395-401.
8. Lane HY, Chiu WC, Chou JC, Wu ST, Su MH, Chang WH. Risperidone in acutely exacerbated schizophrenia: dosing strategies and plasma levels. J Clin Psychiatry 2000;61:209-14.
9. Lane HY, Chang YC, Chiu CC, Lee SH, Lin CY, Chang WH. Fine-tuning risperidone dosage for acutely exacerbated schizophrenia: clinical determinants. Psychopharmacology (Berl) 2004;172: 393-9.
10. Love RC, Conley RR, Kelly DL, Bartko JJ. A dose-outcome analysis of risperidone. J Clin Psychiatry 1999;60:771-5.
11. Jeste DV, Barak Y, Madhusoodanan S, Grossman F, Gharabawi G. International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. Am J Geriatr Psychiatry 2003;11: 638-47.
12. Merlo MC, Hofer H, Gekle W, Berger G, Ventura J, Panhuber I, et al. Risperidone, 2 mg/day vs. 4 mg/day, in first-episode, acutely psychotic patients: treatment efficacy and effects on fine motor functioning. J Clin Psychiatry 2002;63:885-91.
13. Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry 2005; 162:947-53.
14. Kim CY, Shin YW, Joo YH, Hong JP, Lee GH, Choi SK. Risperidone dosing pattern and clinical outcome in psychosis: an analysis of 1,713 cases. J Clin Psychiatry 2005; 66:887-93.
15. Friedman LS, Richter ED. Relationship between conflicts of interest and research results. Gen Intern Med 2004;19:51-6.
16. Kapur S, Remington G, Zipursky RB, Wilson AA, Houle S. The D2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. Life Sci 1995;57:103-7.
17. Nyberg S, Farde L, Halldin C, Dahl ML, Bertilsson L. D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. Am J Psychiatry 1995;152:173-8.
18. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993;13:25-40.
19. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825-35.
20. Claus A, Bollen J, de Cuyper H, Eneman M, Malfroid M, Peuskens J, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand 1992;85:295-305.