Novel antipsychotics and acute dystonic reactions

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Abstract

The growing use of atypical antipsychotics has led to a decrease of acute dystonic reactions (ADR). To evaluate the prevalence of ADR, we recorded all ADR occurring in a population of patients consecutively admitted to a psychiatric intensive care unit. Among 1337 cases treated with antipsychotics, we observed 41 cases (3 – 1%) affected by ADR. At discharge, mean chlorpromazine-equivalent daily dose was 465.8 (± 421.5) mg, while 39 cases (3.0%), all treated with typical neuroleptics, received anticholinergics. Four ADR occurred among the cases treated with risperidone monotherapy, and 4 occurred in risperidone-treated patients after emergency parenteral treatment with typical neuroleptics. In these last 4 cases, temporal relationship suggested that typical neuroleptics had caused ADR. One ADR occurred in a patient treated with olanzapine and 1 ADR in a patient treated with quetiapine. Among cases assuming typical neuroleptics, 32 ADR occurred. The difference between typical and atypical neuroleptics is highly significant ($\chi^2 = 27.756$; d.f. = 1; $p = 0.000$). Atypical antipsychotics carry a minimal risk of ADR.

Introduction

Neuroleptic-induced acute dystonic reactions (ADR) are characterized by sustained abnormal postures or muscle spasms that develop in association with the use of dopaminergic receptor-blocking agents. ADR develop within 7 d (90% within 3 d) of starting, or rapidly raising the dose of anti-dopaminergic drug, or reducing a medication being used to treat or prevent acute extrapyramidal symptoms. ADR are most often localized in the face, neck, and upper part of the body, and rarely involve the lower limbs. They last from seconds to hours and more frequently occur in the afternoon and evening (Mazurek and Rosebush, 1996). Use of high-potency neuroleptics, high dose, parenteral administration of the drug, young age and male gender are established risk factors of ADR (APA, 1997). Other possible risk factors are the following: diagnosis of mania (Nasrallah et al., 1988), higher positive symptoms score (Chakos et al., 1992), higher negative symptoms score and lower Global Assessment Functioning Scale score (Aguilar et al., 1994).

ADR are often distressing and frightening and may even be life threatening when involving laryngeal muscles (Hyman, 1984). Patients with ADR may also present catatonic symptoms and psychotic experiences with a bizarre or dramatic presentation (Thornton and Kenna, 1994). At clinically effective doses, atypical antipsychotics cause fewer extrapyramidal side-effects than typical neuroleptics and carry a minimal risk, or no risk in the case of clozapine, of ADR. In order to assess the true risk of ADR in patients treated with atypical antipsychotics, we registered all cases of ADR that occurred in our Psychiatric Intensive Care Unit (PICU) from 1997.

Patients and method

The study, conducted in accordance with the Declaration of Helsinki, involved all patients consecutively admitted to a 12-bed PICU of a public hospital providing aid to an urban catchment area, between January 1997 and October 2000. Basic characteristics were ascertained for each patient as follows: sex, age, psychiatric diagnoses (according to DSM-IV, based on clinical interviews, review of case notes, and family-history data), current therapy on the first day of hospitalization and on discharge. Current dose of neuroleptic medication was converted to chlor-
promazine equivalents (Baldessarini, 1985). For the novel antipsychotics, the following equivalence was assumed: 100 mg chlorpromazine $\cong 2.5$ mg haloperidol $\cong 50$ mg clozapine $\cong 1.6$ mg risperidone $\cong 3.2$ mg sertindole $\cong 5$ mg olanzapine $\cong 200$ mg quetiapine. The current dose of benzodiazipines was converted to diazepam equivalents (Hyman, 1984), and the current dose of anticholinergic dose to biperiden equivalents (Baldessarini, 1985). As part of standard clinical care on the PICU, whenever possible, we made a more detailed and standardized neuropsychiatric assessment, as soon as possible after admission, using the Expanded Brief Psychiatric Rating Scale, including 24 items rated from 1 to 7 (Ventura et al., 1993), the Scale for the Assessment of Positive Symptoms (Andreasen, 1983), the Scale for the Assessment of the Negative Symptoms (Andreasen, 1981), the Mini Mental State Examination (Folstein et al., 1975), the Global Assessment of Functioning Scale (APA, 1994), the Abnormal Involuntary Movement Scale (National Institute of Mental Health, 1986), the Unified Parkinson's Disease Rating Scale (Fahn et al., 1987), the Barnes Akathisia Scale (Barnes, 1989). Since we could not obtain reliable data about the age of patients at the onset of the disorder, we considered patients' age at first neuroleptic administration as a more reliable indirect measure of length of illness and of neuroleptic exposure. At patients' discharge, we recorded any ADR observed during clinical examination or reported in case sheets or nurses’ reports. Finally, we considered any use of anticholinergics and ascertained the reason of their prescription.

Statistical analysis was conducted by means of $t$ test on continuous variables and $\chi^2$ test on categorical variables; $p < 0.05$ was considered to be statistically significant.

Results

Among 1337 cases admitted in the period of time considered, and treated with antipsychotics, we observed 42 cases (3.1%) affected by ADR and one dubious case that we excluded from analysis. Thirty-two ADR occurred among cases assuming typical neuroleptics and 10 cases among cases assuming atypical neuroleptics. The difference between typical and atypical neuroleptics is highly significant ($\chi^2 = 27.756; d.f. = 1; p = 0.000$).

We were able to complete our standardized neuropsychiatric assessment in 755 (56.5%) cases. In the other cases, this detailed and standardized neuropsychiatric assessment was not possible because of early discharge, transfer to other PICU for administrative reasons or, in a minority of cases, patients’ refusal to participate. At discharge, mean daily antipsychotic dose (expressed in chlorpromazine equivalents) was $471.4 (\pm 317.7)$ mg in the ADR group and $456 (\pm 408.8)$ mg in the non-ADR group (ns, $p = 0.819$). To treat emerging extrapyramidal side-effects, 39 cases (3.0%) (all treated with typical neuroleptics) received anticholinergics (in almost every case, 4 mg of biperidene p.o., daily). Patients who presented ADR were treated with 4 mg biperidene p.o. or i.m. During hospitalization, 15 cases received quetiapine, 19 sertindole, 95 olanzapine, 142 clozapine, 495 risperidone and 561 typical neuroleptics. Among the cases treated with antipsychotic risperidone mono-therapy, 4 ADR occurred (daily doses of 2, 3, 3 and 4 mg). Among all cases receiving risperidone, we observed 4 ADR after emergency parenteral treatment with typical neuroleptics. In all these cases, temporal relationship suggested that typical neuroleptics had caused ADR. One patient treated with olanzapine (20 mg/d) presented a long lasting, dose-dependent dystonia of the neck. In the past, this patient had presented a severe long-lasting tremor during treatment with sertindole and lithium (Raja, 1998b). Her neck dystonia quickly recovered when olanzapine was withdrawn and substituted with 50 mg/d of clozapine. One patient presented a long-lasting dystonia of the trunk (Pisa syndrome) after treatment with risperidone (3 mg/d). The patient immediately recovered after withdrawal of the offending drug but presented the same symptoms after treatment with 600 mg/d of quetiapine. The patient’s dystonia disappeared when we tapered the daily dosage of quetiapine to 300 mg/d.

In summary, we observed ADR in 8 out of 495 cases (1.6%) treated with risperidone. However, in 4 cases the clinical context suggested that ADR had been caused by typical neuroleptics concomitantly administered. That points to a very low prevalence (0.8%) of ADR in cases treated with risperidone as sole antipsychotic. Olanzapine caused one ADR among 95 treated cases and quetiapine caused one ADR among 15 treated cases. No ADR occurred among the 19 sertindole-treated cases or among the 142 clozapine-treated cases.

Cases with ADR were significantly younger [33.7 ($\pm 11.6$) yr vs. 42.0 ($\pm 14.1$) yr; $t = -3.729$; d.f. = 1327; $p = 0.000$] and had started their first neuroleptic treatment significantly more recently [4.5 ($\pm 5.4$) yr vs. 10.8 ($\pm 11.1$) yr; $t = -3.087$; d.f. = 573; $p = 0.002$] than non-ADR cases. The male/female ratio was higher in the group with ADR, however, the difference failed to reach statistical significance (25/17 vs. 567/727; $\chi^2 = 3.455$; d.f. = 1; $p = 0.063$). Furthermore, ADR cases’ length of hospitalization was significantly higher than the length of hospitalization of non-ADR cases [18.7 ($\pm 14.3$) d vs. 12.3 ($\pm 13.6$) d; $t = 2.996$; d.f. = 1317; $p = 0.003$]. Finally, the diagnosis of delusional disorder was significantly more frequent in the group with ADR [4
(9.5%) vs. 15 (1.2%); $\chi^2 = 14.774$; d.f. = 1; $p = 0.000$. Otherwise, the groups with and without ADR appeared similar.

Discussion

The weaknesses of the open, uncontrolled study should be noted. Although, we made every effort to avoid under-reporting of ADR, we were not able to directly observe the patients during the whole time of their hospitalization. Although the differential diagnosis is extensive (Raja, 1998a), the diagnosis of ADR is usually obvious, at least in clinically significant cases. In this sample, we considered the diagnosis of ADR to be dubious in just one case, which we excluded from analysis. However, mild cases of ADR may not be so easily recognized, especially by professionals lacking experience in movement disorders. Caution is recommended in considering the reported prevalence of ADR in a population of psychiatric inpatients since, unavoidably, during the course of the day, most ADR are observed and reported by professionals with various clinical experience in movement disorders.

The most important result of our study is the much lower prevalence of ADR in patients treated with atypical antipsychotics in comparison with patients treated with typical neuroleptics. The difference between the two groups of patients is highly significant, especially considering that patients known to have sensitivity to extrapyramidal symptoms are more likely to be treated with atypical compounds. In our sample, we found that ADR were significantly more frequent in young patients (especially males) who had started their first neuroleptic treatment significantly more recently than non-ADR cases. These results are in accordance with published studies. Neuroleptic-induced ADR are 15 times more common in patients under 35 years of age (Addonizio and Alexopulos, 1988). Among patients above 50 yr, men are twice as likely as women to develop ADR. On the contrary, the ADR rate in patients older than 50 yr is similar in men and women (Sweet, 1975). The highest incidence rate was found in a population of high-risk young male patients (Boyer et al., 1987). Not surprisingly, the length of hospitalization was significantly higher in the group of ADR cases. Some early-discharged cases had not spent the entire time of risk of developing ADR in the ward and could have presented ADR after discharge.

An unexpected result is the strong association that we found between ADR and the diagnosis of delusional disorder. To our knowledge, no other study has reported such an association; however, the result appears plausible. In contrast with other psychotic disorders, delusional disorder is characterized by minimal response to antipsychotics. This probably reflects a different pathogenesis of delusional disorder not involving hyperactivity of brain dopaminergic circuits and could account for the hypersensitivity to the side-effects of anti-dopaminergic drugs typically observed in patients with this diagnosis.

Growing evidence shows that atypical antipsychotics carry a minimal risk of ADR (Raja and Azzoni, 2000; Stanniland and Taylor, 2000). ADR induced by risperidone have been described, however, their frequency seems to be lower in comparison with typical neuroleptics (Faulk et al., 1996). At McLean Hospital and the Massachusetts Mental Health Center, Schatzberg et al. (1997) reported that ADR were somewhat less common with risperidone in relation to standard antipsychotics. At our hospital, we saw a very low prevalence of ADR in cases treated with risperidone (0.8%), olanzapine (1.1%), sertindole (0%), clozapine (0%). The number of cases treated with quetiapine is so small that it seems of little use to consider the percentage. Furthermore, the only two cases treated with olanzapine or quetiapine who presented ADR had been unusually sensitive to extrapyramidal side-effects of previous anti-dopaminergic treatment, including risperidone. For these patients, we had chosen olanzapine and quetiapine for their excellent profile to prevent further neurological side-effects.

To avoid panic reactions and to prevent future poor compliance to treatment, patients starting antipsychotic treatment should be warned against the possible manifestation of ADR, and should receive instructions on how to manage them adequately. However, ADR may induce trouble and anxiety even in informed patients.

Unfortunately, ADR occur in a significant percentage of patients, even at low doses (APA, 1997) and there is no way to foresee which patients are going to suffer from this side-effect. For this reason, in the era of typical neuroleptics, many clinicians preferred to prescribe anticholinergics from the outset. APA guidelines (APA, 1997) suggested that prophylactic anticholinergics should be considered especially for patients treated with high potency agents who have a prior history of acute extrapyramidal side-effects, those who prefer preventive treatment to avoid discomfort or distress, or those for whom the occurrence of side-effects would lead to poor compliance. A WHO consensus statement (WHO, 1990) suggested a prophylactic utilization of these agents in the first weeks of treatment to prevent ADR. Thereafter, anticholinergics should be withdrawn and the indication to their use should be re-evaluated. The need of anticholinergic treatment should also be re-evaluated when the neuroleptic dose is lowered. The much lower prevalence of ADR among patients treated with atypical antipsychotic agents suggests no prophylactic use of anticholinergics in these patients. When ADR appear in
patients treated with atypical antipsychotics, the following two options are conceivable, after possible immediate and sporadic acute treatment with anticholinergics: (1) to reduce the dose of the offending drug; (2) to switch to another atypical antipsychotic agent with lower risk of ADR. We always prefer to avoid the concomitant use of anticholinergics in patients treated with atypical antipsychotics, since, in our opinion, this minimizes some potential advantages of these new and more expensive drugs. Anticholinergics have side-effects (e.g. tachycardia, mydriasis, urinary retention, constipation), potentially dangerous for patients with heart disease, glaucoma, prostatic disease, or ileus, and impair cognitive function, especially in the elderly. Anticholinergics worsen the severity of tardive dyskinesia and may even produce psychotic exacerbation (Faulk et al., 1996; Johnstone et al., 1983). Furthermore, several patients tend to abuse these drugs. Caution is warranted in prescribing anticholinergics to patients with serious risk of suicide because of the toxicity of an anticholinergic overdose.

Undoubtedly, the growing utilization of atypical antipsychotics as first-line treatment of psychotic disorders caused a dramatic decrease in the rate of ADR and make unnecessary the prophylactic use of anticholinergics. Even in the infrequent cases of ADR induced by atypical antipsychotics, anticholinergics are probably avoidable since the phenomenon is short-lived and rarely recurs. However, since the novel antipsychotics are expensive and currently unavailable in injectable form, a significant number of acute psychotic patients will continue to take conventional neuroleptics and to suffer from ADR.

References


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