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A naturalistic study: 100 consecutive episodes of acute agitation in a psychiatric emergency department

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Introduction. Psychomotor agitation is a common event in psychiatric emergency services (PES) with a prevalence of approximately 10 %. There is no general consensus on to how to manage psychomotor agitation; benzodiazepines, typical antipsychotics and now atypical antipsychotics have demonstrated similar efficacy. The aim of our study was to describe the epidemiology and clinical management of agitation in «real-life» in a psychiatric emergency service.

Methods. A naturalistic study was performed in acutely agitated patients recruited consecutively in a psychiatric emergency service. Demographics, clinical and therapeutic characteristics were analyzed. Efficacy was assessed by the Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC) and the Agitation-Calmness Evaluation Scale (ACES). Pragmatic variables such as the need for second pharmacological intervention and the need for physical restraints were assessed.

Results. The study included 100 patients with psychomotor agitation. Mean age was 36.2 % and 54 % were women. The most prevalent diagnoses were psychotic disorder (48 %) and personality disorder (24 %). Physical restraint was required in 39 % of patients and 52 % accepted oral treatment. Haloperidol was the most frequent oral treatment and olanzapine was the most frequent intramuscular treatment.

Conclusions. A naturalistic approach provides data based on clinical reality in psychiatric emergency services. Strict research designs of clinical trials of efficacy imply sample selection biases and are generally distanced from the clinical reality. Atypical antipsychotics have become the first-line treatment in acute agitation.

Key words:
Acute agitation. Pharmacological treatment. Naturalistic study.

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Estudio naturalístico: 100 episodios de agitación psicomotriz consecutivos en urgencias psiquiátricas

Introducción. La agitación psicomotriz es una situación frecuente en urgencias de psiquiatría con una prevalencia aproximada del 10 %. No hay un consenso total respecto a su manejo; benzodiazepinas, antipsicóticos típicos y, más recientemente, los atípicos han demostrado una eficacia similar. El objetivo del presente estudio es describir las características epidemiológicas y el manejo clínico de los pacientes agitados en la práctica clínica en un servicio de urgencias psiquiátricas.

Métodos. Estudio naturalístico de los episodios de agitación psicomotriz recogidos consecutivamente en un servicio de urgencias psiquiátricas. Se recogieron variables demográficas, clínicas y terapéuticas. Las variables de eficacia fueron la escala *Excitement Component of the Positive and Negative Syndrome Scale* (PANSS-EC) y la *Agitation-Calmness Evaluation Scale* (ACES). Se analiza variables pragmáticas como la necesidad de sucesivas intervenciones farmacológicas o la necesidad de contención física.

Resultados. Fueron incluidos 100 episodios de agitación psicomotriz. La edad media fue de 36,2 años y el 54 % eran mujeres. Los diagnósticos más frecuentes fueron de trastorno psicótico (48 %) y de trastorno de la personalidad (24 %). El 39 % requirió contención física y el 52 % aceptó el tratamiento por vía oral. El haloperidol fue el fármaco más utilizado por vía oral y la olanzapina por vía intramuscular.

Conclusiones. Una aproximación naturalística permite obtener datos de la práctica real en los servicios de urgencias psiquiátricas. Los estrictos diseños de investigación de los ensayos clínicos de eficacia implican sesgos de selección de la muestra y se suelen alejar de la realidad clínica. Los antipsicóticos atípicos se están convirtiendo en fármacos de primera línea en el tratamiento de la agitación.

Palabras clave:
Agitación psicomotriz. Tratamiento farmacológico. Estudio naturalístico.

INTRODUCTION

Psychomotor agitation, whose prevalence is approximately 10 %, is a frequent situation in the psychiatric emergency service[1]. It causes a marked malaise for the patient and is generally accompanied by hostility and destructive and/or aggressive behaviors. Thus, it often requires physical restraint measures, that may cause the patient traumatic experiences and affect future therapeutic alliance with the professionals[2,3]. Consequently, immediate, effective intervention that permits rapid control of the symptoms is essential in an agitated patient.

Historically, agitation was basically controlled with physical restraint. With the appearance of pharmacotherapy, treatment considerably improved, thus decreasing the need for physical measures. Different drugs have been used, however a consensuated protocol regarding pharmacological treatment of psychomotor agitation presently continues to be lacking[3,4]. Benzodiazepines have shown their efficacy in treatment of agitation[5,6]. However, they may cause excessive sedation and respiratory depression, ataxy, disinhibition and confusion[5,7]. There is a greater risk of appearance of these adverse effects when the patient has consumed alcohol or toxic agents or when they are administered in combination with typical antipsychotics and/or intravenously[4,8]. Conventional oral or parenteral antipsychotics have been the therapeutic strategy generally used to control agitated psychotic patients[3,4]. However, they may cause dysphoria, serious extrapyramidal symptoms such as acute dystony in 25 % of the patients[5,9] and akathisia[10]. Atypical antipsychotics are presently the drugs of choice for the treatment of schizophrenia and acute mania due to their better tolerability and lower risk of side effects[11]. The studies published indicate that they are also effective drugs in oral and intramuscular treatment of psychomotor agitation[12,13].

Based on a survey conducted to coordinators of psychiatric emergency services in the USA, Currier et al.[14] reflected that 8.5 % of the patients who came to the emergency services required physical restraint with a mean duration of 6.1 hours. In 70.3 % of the agitation cases, a «cocktail» of haloperidol, benzodiazepine and anticholinergic agent was used. The intramuscular formula was preferred by 64 % of the coordinators, although only 10 % of the patients required involuntary intramuscular treatment. On the other hand, in a survey on the preferences of patients who come to the psychiatry emergency services[15], they preferred drug treatment to physical restraint, oral to intramuscular treatment and the preferred drug by the patients was benzodiazepines, typical neuroleptics being the last option.

In our setting, the therapeutic options in these situations have increased in the last two years with the appearance of new formulations of atypical antipsychotics such as orodispersable or intramuscular olanzapine, resperidone in solution and intramuscular ziprasidone. No epidemiology study exists in our country on the pharmacological treatment and management usually employed in the psychiatric emergency services.

A naturalistic approach allows us to obtain data from the real practice since strict designs of research are generally distanced from the daily clinical reality. This present study aims to describe the epidemiological characteristics and clinical management of agitated patients in the usual clinical practice in a psychiatric emergency service.

MATERIAL AND METHODS

A naturalistic study of the psychomotor agitation episodes seen consecutively from June 2004 to October 2004 in the psychiatric emergency service of the Hospital de la Santa Creu i Sant Pau of Barcelona was conducted. This emergency service is a facility located independently from the remaining hospital emergency services and has two observation/restraining rooms, one nursing control, one medical office and one waiting room. Its staff is made up of a psychiatry staff member, part time psychiatry resident, psychiatry nurse and assistant.

The only enrolment criterion was the consideration by the service staff that the patient was in a state of agitation according to the following definition: motor exaltation state (restlessness, gesticulation, ambulation, etc.) made up of automatic or intentional movements, but which generally lack an objective[16].

Demographic, clinical and therapeutical variables are collected. Efficacy variables were the Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC) (17) whose items are: excitement, hostility, motor tension, uncooperativeness and poor impulse control with a total score ranging from 5 (absence of agitation) to 35 (maximum severity); and Agitation Calmness Evaluation Scale (ACES) (copyright Eli Lilly and Company, 1998). This is a 9 point scale developed by Eli Lilly and Company where 1 indicates marked agitation; 2, moderate agitation; 3, mild agitation; 4, normal behavior; 5, mild calmness; 6, moderate calmness; 7, marked calmness; 8, deep sleep, and 9, non-evaluable. General psychopathological state of the patient was evaluated with the Clinical Global Impression-Severity (CGI-S) scale[18]. Furthermore the following pragmatic variables were collected: need for successive pharmacological interventions and need for mechanical restraint.

The data were analyzed with the SPSS version 11.0 statistical program. For categoric variables, the chi square and Student's *t* test for quantitative variables were used. All the analyses were done by intention to treat, using the Last Observation Carried Forward (LOCF) method. Analysis of the variance for repeated measurements (ANOVA) was used to evaluate efficacy.

RESULTS

Clinical and demographic characteristics

During the 5 months the study lasted, 2,324 patients visited the psychiatric emergency service of the Hospital de la Santa Creu i Sant Pau, 100 (4.3 %) of whom had an agitation episode. These 100 episodes were included in the study consecutively. Table 1 shows the demographic and clinical characteristics of the patients. The sample was made up of 46 men and 54 women whose mean age was 36.2 years (SD: 13.4; range: 15-75). The most frequent diagnoses were psychotic disorders (48 %) and personality disorders (24 %). In regards to clinical severity, mean score on the PANSS-EC was 24.3 (SD 5.3) and on the ACES 2.2 (SD 0.7) that corresponds to moderate severity was observed. Mean score on the CGI-S was 5.5 (SD 1.0).

Physical restraint was necessary from the onset in 39 % of the patients due to risk of hetero- or self-aggressive behaviors. Drug treatment was necessary in every case. A total of 52 % of the patients accepted oral treatment while 48 % of the patients chose intramuscular treatment.

Toxic agents in urine were measured in 21 cases and 5 cases were positive for alcohol, 7 for cannabis, 4 for cocaine and 1 for opiates.

Pharmacological intervention

Table 2 shows the drugs used in the 52 patients who accepted oral treatment. The mean PANSS-EC of the patients treated orally was 23.3. Seventeen (32.7 %) of the patients required physical restraint and a single drug intervention was sufficient in 56 % of the cases. Haloperidol was administered to 20 patients with a mean dose of 11.5 mg and range between 5-20 mg. Seventeen patients were administered orodispersable olanzapine with a mean dose of 15.6 mg and range between 5-20 mg. Treatment with benzodiazepines (mainly clonazepam and clorazepate dipotassium) was chosen in 8 patients, risperidone in 4 cases and the combination of conventional antipsychotics plus benzodiazepines was used in 3 patients.

Table 3 shows the treatments prescribed when intramuscular administration of the drug was considered necessary (n = 48). The mean PANSS-EC of clinical severity was 25.4, 45.8 % initially required physical restraint and efficacy of the first intervention was 83 %. The intramuscular drug used most was olanzapine in 45.8 % of the cases and haloperidol was used in second place in 25 % of the subjects. Intramuscular ziprasidone was used in seven patients, benzodiazepines (clorazepate dipotassium 50 mg) in one case and the combination of conventional antipsychotics with benzodiazepines or with sedative profile antipsychotics in six patients.

Table 1 Demographic and clinical characteristics of the sample

Sample (n = 100)	
Age/years (SD/range)	36.2 (13.4/15-75)
Gender (% women)	54 %
Diagnostic orientation	
Psychotic disorder	48 %
Bipolar disorder. Manic episode	9 %
Anxious-depressive disorder	7 %
Personality disorder	24 %
Toxic consumption disorder	4 %
Others	8 %
Need for physical restraint	39 %
Oral treatment	52 %
PANSS-EC (SD/range)	24.3(5.3/18-35)
ACES (SD/range)	2.2 (0.7/1-3)
CGI-S (SD/range)	5.5 (1.0/4.7)

Table 2 Oral pharmacological intervention (n = 52)

Drug	N	Need for restraint	PANNS-EC (range)	Mean dose mg (range)	Need for 2nd intervention
Haloperidol	20	11/20	25.8 (19-33)	11.5 (5-20)	10 /20
Olanzapine	17	6/17	22.7 (18-31)	15.6 (5-20)	6/17
Risperidone	4	0/4	21.0 (18-28)	4 (3-5)	2/4
Benzodiazepines	8	0/8	21.0 (15-28)		5/8
Cocktail	3	0/3	19.7 (16-22)		0/3

Mean PANSS-EC: 23.3. Need for physical restraint: 17 patients (32.7 %).

Table 3 Intramuscular pharmacological intervention (n = 48)

Drug	N	Need for restraint	PANNS-EC (range)	Mean dose mg (range)	Need for 2nd intervention
Olanzapine	22	7/22	25.8 (19-33)	10.5 (10-20)	5/22
Haloperidol	12	10/12	29.1 (25-35)	9.1 (5-15)	2/12
Ziprasidone	7	0/7	19.8 (18-25)	20	0/7
Benzodiazepines	1	0/1	17		0/1
Cocktail	6	4/6	28 (21-35)		2/6

Mean PANSS-EC: 25.4. Need for physical restraint: 22 patients (45.8 %).

Table 4 Differences between profile of patients receiving oral treatment and those administered intramuscular treatment

	Oral route (n = 52)	Intramuscular route (n = 48)	*p*
Age*	36.9	35.5	ns
Diagnosis of psychosis**	26	22	ns
Need for restraint**	17	22	ns
Total PANSS-EC*	23.3	25.4	0.05
ACES*	2.4	2.0	0.05

*T-test. **Chi square.

Table 4 shows the differences between the profile of the patients receiving oral treatment versus intramuscular. No significant differences were observed regarding age, diagnostic orientation or need for physical restraint. Patients who received intramuscular treatment had greater clinical severity with statistically significant differences on the total PANSS-EC and ACES scales.

A significant reduction in mean score of PANSS-EC (baseline score 24.32, at 14.22 h; at 2 hours 10.61, and at 4 h, 9.85) (F: 166.95; gl: 2.72; p = 0.000) was observed using the ANOVA analysis with the LOCF method. No comparative analysis was done between oral and intramuscular treated patients since these samples had enrolment biases and were non-comparable. A tendency to faster improvement in the intramuscular treated patients than those treated orally was observed (fig. 1).

The possible differences in the profiles of patients receiving treatment with conventional antipsychotics or in whom treatment with atypical ones was decided were also analyzed (table 5). Patients who received treatment with typical antipsychotics had greater clinical severity on the PANSS and ACES scales, greater frequency of diagnosis of psychosis and greater need for physical restraint.

Safety

No serious adverse event occurred. Two cases of excessive sedation were observed with oral haloperidol and there was one case of dystony, two of excessive sedation and one patient who complained of dizziness with the intramuscular administration. Anticholinergics were administered in two subjects to prevent extrapyramidal effects. Two cases of excessive sedation were recorded with intramuscular olanzapine and one case had hypotension with intramuscular ziprasidone, although it was well tolerated (diastolic pressure of 40). Excessive sedation and hypotension (diastolic pressure of 30) were observed with the combination of intramuscular levomepromazine and haloperidol in two cases.

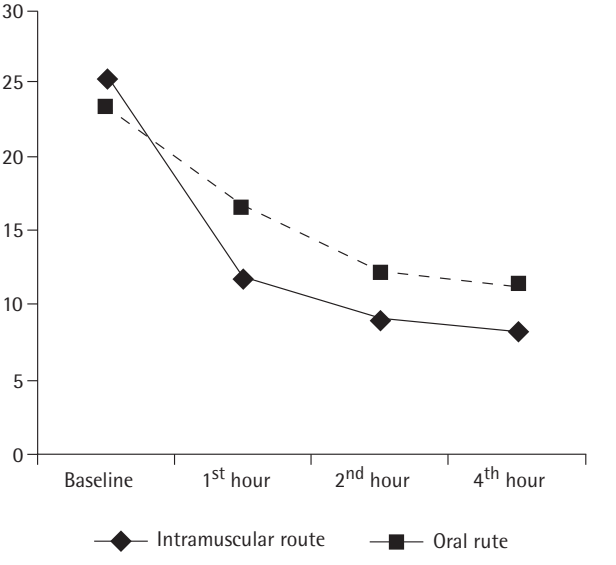

Figure 1 *Changes in mean score of the PANSS-EC according to administration route. Pre and post-treatment ANOVA analyses with Last Observation Carried Forward (LOCF). Intramuscular route: F: 154,23; gl: 2,27; p = 0,000. Oral route: F: 54,85; gl: 2,33; p = 0,000.*

CONCLUSIONS

A naturalistic approach makes it possible to obtain data focused on the clinical practice. Clinical trials, generally financed by the pharmaceutical industry, are essential to demonstrate the efficacy and safety of a new drug. However,

Tabla 5 Differences between profiles of patients receiving typical antipsychotic treatment (in monotherapy or combination) versus atypical antipsychotics

	Typical AP (n = 39)	Atypical AP (n = 52)	*p*
Age*	36.1	35.3	ns
Diagnosis of psychosis**	25	21	0.03
Need for restraint**	24	14	0.01
Total PANSS-EC*	26.8	23.1	0.00
ACES*	2	2.4	0.01

*T-test. **Chi square.

the strict designs of research often cause the patients to be not representative of the real population seen in the emergency services[2]. Clinical trials generally exclude severely agitated, elderly patients with medical comorbidity or patients who do not sign the informed consent. These drugs of «proven efficacy» are not so proven in the clinical practice with «real patients.» Thus, subsequent pragmatic studies to describe their effectiveness are necessary[19]. The objective of the study is to describe pragmatically the management of agitation in the psychiatric emergency service in our setting.

Clinical trials on agitation generally only include psychotic or manic patients and generally exclude severe agitations or other diagnoses, especially personality disorders, that account for up to 40 % of the cases[13]. In our study, as there are no limitations in severity, age or diagnosis, we obtained a sample with characteristics more adequate for «real patients» than those generally seen in the emergency services. They are agitated patients with moderate-severe clinical severity (PANSS-EC = 24.3), with a very wide age range going from 15 to 75 years. Furthermore, although most were patients with psychotic disorders (48 %), there was a low proportion of manic patients (9 %) and high proportion of patients with personality disorders (25 %). One piece of information to consider is the limited proportion of intoxicated patients (8 %) observed in our sample. This is because the patients with suspicion of intoxication are seen in medical emergencies[16] and do not reach psychiatry due to our hospital's protocols.

In our sample, only 39 % of the agitated patients required mechanic restraint and more than half of the cases received oral treatment. However, it must be stated that oral treatment does not always mean voluntary treatment. A possible explanation would be that the psychiatric emergency Service of the Hospital de la Santa Creu i Sant Pau is located independently from the general emergency services, has specialized nursing staff in psychiatry and specific safety measures to prevent aggressiveness episodes.

When oral drug intervention was used, although typical antipsychotics such as haloperidol continue to be the drugs used most (38.5 %), a noticeable use of atypical antipsychotics with new formulations such as orodispersable olanzapine (32.7 %) or risperidone in solution (7.7 %) was observed. It should be stated that oral benzodiazepines were used as first choice in only 15.4 % of the cases.

Intramuscular treatment was chosen in 48 % of the patients. The drug used most was the new formulation of intramuscular olanzapine (45.8 %). In 77.3 % of the cases, this was effective with a single intervention, followed by haloperidol and then by intramuscular ziprasidone. Intramuscular benzodiazepines were only used in one case and the «cocktail» or combination of typical antipsychotics plus benzodiazepines or sedative antipsychotics were only used for the six severest cases.

Patients treated intramuscularly had a profile that was more severe with a higher score on the PANNS-EC and ACES scales. When the clinical course was analyzed according to the route used, patients who required the intramuscular route were more serious but had faster improvement in the first hour of treatment and only 17 % needed a second intervention. Patients treated orally were less serious, improvement in the first hour was slower and a second intervention was needed in 44.2 %. Although the action protocols in agitated patients recommend oral treatment as the first option to avoid traumatic experiences against the will of the patient[3], intramuscular treatment would be a faster intervention with less need for new interventions according to our results.

With the appearance of new atypical antipsychotic formulations, these drugs were chosen as the first treatment option in more than half of the agitations in spite of lacking indication for many other cases, such as intoxicated patients or those without diagnosis of psychotic disorder or manic episode. However, in patients with psychosis diagnosis, with severe clinical severity and requiring mechanical restraint more frequently, treatment with typical antipsychotics continued to be preferred. Absence of serious adverse effects also stands out and extrapyramidal effects were very rare (one single case of acute dystony).

The pragmatic variables used in this study seem to be useful to determine the effectiveness of the therapeutic interventions made. To be able to distinguish the possible superiority of any of them in treatment of agitation episode, a larger population must be studied, assigning the patients consecutively admitted to hospital randomly to one of the mentioned pharmacological options and assessing their effectiveness by the need to repeat the therapeutic intervention and requirement of mechanical restraint after the first dose.

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