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Efficacy and safety of intranasal haloperidol in an acute Psychiatry Unit: a pilot study on schizophrenic patients with mild-modedate agitation

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ABSTRACT

Aim. To study the efficacy and safety of intranasal administration of 5 mg haloperidol on mild-moderate agitated patients with schizophrenia or schizoaffective disorder in an acute psychiatry unit setting.

Method. Design: Pilot study of clinical trial, phase IV, open-label, observer-blind, single-center, randomized a haloperidol-controlled trial comparing intranasal with intramuscular administration. Subjects: 16 patients; 7 intranasal administration, and 9 intramuscular administration. Efficacy measurement: Positive and Negative Syndrome Scale-Excited Component (PANSS-EC); Clinical Global Impressions-Improvement Scale (CGI). Safety measurement: Changes in the ECG registered 5 minutes pre-treatment and 5 minutes post-treatment.

Results. Intranasal administration showed more quick action compared with intramuscular on the PANSS-EC (p=0.042) and CGI (p=0.041) 10 minutes after administration, with similar efficacy up to 20, 30, and 60 minutes. There were no significant differences between QTc baseline and post-treatment.

Conclusion. Intranasal haloperidol was a rapid, effective, and well-tolerated alternative for reducing acute mild-moderate agitation.

Key words. Intranasal haloperidol, schizophrenia, schizoaffective disorder, psychomotor agitation, emergency.

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EFICACIA Y SEGURIDAD DEL HALOPERIDOL INTRANASAL EN UNA UNIDAD DE AGUDOS: ESTUDIO PILOTO EN PACIENTES ESQUIZOFRÉNICOS CON LEVE-MODERADA AGITACIÓN

RESUMEN

Objetivo. Estudiar la eficacia y seguridad de la administración de 5 mg de haloperidol intranasal en pacientes con esquizofrenia y trastorno esquizoafectivo, con leve o moderada agitación, ingresados en una unidad de agudos de psiquiatría.

Método. Diseño: Estudio piloto de ensayo clínico, fase IV, con evaluador ciego, unicéntrico, aleatorizado y controlado de grupos paralelos, comparando la administración intranasal con la intramuscular. Sujetos: 16 pacientes; 7 administración intranasal y 9 administración intramuscular. Medidas de eficacia: Escala de Síntomas Positivas y Negativos-Componente Excitación (PANSS-EC); Escala de Impresión Clínica Global (CGI). Medidas de seguridad: Cambios en el ECG registrados 5 minutos pretratamiento y 5 minutos postratamiento.

Resultados. La administración intranasal mostró mayor rapidez de acción en comparación con la intramuscular en la PANSS-EC (p = 0,042) y la CGI (p = 0,041) a los 10 minutos de la administración, con similar eficacia a los 20, 30 y 60 minutos. Sin diferencias significativas en el QTc basal y postratamiento.

Conclusión. El haloperidol intranasal fue una alternativa rápida, efectiva y bien tolerada para reducir la agitación leve-moderada en estos pacientes.

Palabras clave. Haloperidol intranasal, esquizofrenia, trastorno esquizoafectivo, agitación psicomotriz, emergencia.

INTRODUCTION

Psychomotor agitation in psychiatric patients is a cognitive and motor hyperactive state characterised by excitability, irritability and psychomotor restlessness. It can lead to verbal and physical aggression and is considered an emergency. Over 10% of psychiatric interventions are due to psychomotor agitation, which is particularly prevalent in patients with schizophrenia (11%). Its proper management can reduce the risk of escalation towards aggression and violence[1].

Agitated patients associated with a psychotic syndrome, admitted to an acute unit, should preferably be managed with antipsychotic drugs, whose route of administration and onset of action is fast, effective and safe. Haloperidol is a first-generation antipsychotic, of the butyrophenone class, and is widely used as one of the drugs of choice for the treatment of agitation in psychiatric patients[2]; it is administered by the intramuscular (IM) route and recommended in international clinical guidelines[3,4]. Although the therapeutic onset time via the IM route is shorter than for the oral formulation, it may be too long to prevent the agitation symptoms from becoming significantly worse[5].

The intranasal route (IN) has been useful in an emergency setting to calm agitated patients with drugs such as midazolam and ketamine[6]. This route is an alternative to consider for the following reasons: it avoids the pain and emotional stress of inserting the needle; it is quick acting, due to its rapid absorption in the widely vascularised nasal cavity, whose olfactory tract leads directly to the central nervous system; and it avoids first-pass liver metabolism. Miller et al.[5] published a pilot study with 4 healthy volunteers comparing IN administration haloperidol pharmacokinetics with intravenous (IV) and IM administration. Each subject received 2.5 mg haloperidol with a random choice of route. Peak concentration was achieved 15 minutes after IN and IV administration and 37.5 minutes after IM, which shows that IN absorption is rapid, and had clinically significant drug plasma levels [9.8 ng/mL (IN), 8.4 ng/mL (IM), 23.3 ng/mL (IV); therapeutic range 5-15 ng/mL].

Our objective was to study the safety and efficacy of 5 mg haloperidol IN administration in patients with schizophrenia and schizoaffective disorder, with mild or moderate agitation admitted to an acute psychiatric unit. Our hypothesis was that the IN route is just as safe as the IM route but with a quicker sedation onset time.

METHOD

This is a pilot study of a phase IV, controlled, single-centre clinical trial, randomised by interchanging variable size blocks of parallel groups with a blind evaluation. The sample was taken from the years 2016 and 2017, and consisted of adults between 18 and 65 years old with a diagnosis of schizophrenia and schizoaffective disorder (DSM-5)[7]. They were admitted to the Hospital Parc Taulí Acute Psychiatry Unit in a state of psychomotor agitation and were indicated treatment with an IM antipsychotic. All signed the informed consent to participate in the study. Those patients with exacerbated comorbid medical pathology and other psychiatric diagnoses (except for cannabis abuse) were excluded; as well as those who had been administered a depot antipsychotic during the previous month. The last dose of prescribed psychotropic drugs was not administered during admission, in order to objectify the effect of haloperidol and avoid possible drug interactions. The patients were evaluated during the 60 minutes after the agitation episode and administration of the drug. The 16 patients were randomised and administered 5 mg of haloperidol (using a 5 mg/mL injectable solution): 9 via IM and 7 via IN. For the IN administration, the patient lay on a bed in a supine position with his head inclined at a 45° angle. A diffuser was added to a standard 5 mL syringe and the patient asked to breathe in as the haloperidol was administered via the syringe and diffuser.

Clinical efficacy was measured by subtracting the baseline scores previously of treatment administration from the scores obtained at 10, 20, 30 and 60 minutes for the PANSS-EC[8] and the CGI-I[9]. The PANSS-EC scale is composed of 5 items: excitement, tension, hostility, uncooperativeness and poor impulse control. Each item scores from 1 (not present), 2 (minimal), 3 (mild), 4 (moderate), 5 (moderately severe), 6 (severe) to 7 (extremely severe). The evaluation is obtained from the sum of each item, with a mean score of ≥ 20 corresponding to clinically severe agitation. The CGI scale evaluates severity of the condition from a single item of values ranging from 0 (normal) to 7 (extremely ill). Safety was assessed by subtracting the baseline heart rate and blood pressure values from those obtained at 10, 20, 30 and 60 minutes, as well as changes in the ECG recorded 5 minutes before and 5 minutes after treatment administration.

The Mann Whitney U test was applied for the non-parametric variables and Student's t test for the parametric variables, with significance being $p < 0.05$. The clinical trial was approved by the hospital Ethics Committee and permits were obtained from the Spanish Medicines Agency.

RESULTS

The socio-demographic and clinical details of the patients with mild-moderate psychomotor agitation treated with IN haloperidol are shown in Table 1. Table 2 shows the patient PANSS-EC and CGI scale scores, with IN haloperidol

showing quicker improvement in symptoms (PANSS-EC and CGI) than IM at 10 minutes; although both routes had a similar response at the remaining time points (20, 30 and 60 minutes). The treatment efficacy measured by PANSS-EC is shown in Figure 1, and compares the improvement in symptoms (PANSS-EC) at 10 minutes via the IN route with the IM route, with a similar response for both administration routes being seen at the rest of the time points. The blood test performed at hospital admission (leukocyte formula, kidney and liver function) was within normality. In six cases, cannabis was positive in the urine toxins test. The pharmacological treatment of patients during admission is shown in Table 1. All patients collaborated in the administration of haloperidol. Only one case required extra medication (5 mg haloperidol IM route) due to the persistence of the agitation symptoms. Two of the patients treated by the IN route complained of lachrymation. A minimal, non-pathological prolongation of the QTc (defined as QT > 436 ms)[10] was detected in both

Table 1 Sociodemographic and clinical data of patients with psychomotor agitation treated with haloperidol

	IM group n = 9	IN group n = 7	p-valor
SOCIODEMOGRAPHIC DATA			
	Mean (SD)		
Age	39,9 (11,3)	37,6 (13,1)	p = 0,710
Gender (Male)	7	7	
Civil Status (Single)	7	7	
Education (Basic)	8	8	
Employment status (Active)	3	2	
CLINICAL DATA			
DSM-5 Diagnostics			
Schizophrenia	6	6	
Schizoaffective Disorder			
Bipolar Type	3	1	
Cannabis use disorder	4	2	
Body Mass Index	26.9 (4.5)	24.3 (4.4)	0.269
PHARMACOTHERAPY			
Atypical antipsychotic	8	4	
Mixed antipsychotic	1	3	
Stimulants	2	2	
Benzodiazepines	7	4	
Anticholinergics	1	1	
EFFICACY			
Post-treatment changes	median (25th, 75th percentiles)		
Positive and Negative Symptom Scale-Excited Component (PANSS-EC)			
0 min (baseline)	17 (15.5, 20.5)	17 (16.0, 22.0)	
10 min	1 (-0.5, 6.0)	6 (4.0, 7.0)	0.042*
20 min	5 (3.0, 6.5)	6 (6.0, 11.0)	0.091
30 min	6 (4.0, 6.5)	6 (5.0, 9.0)	0.408
60 min	6 (2.0, 8.0)	6 (5.0, 10.0)	0.470

	M group n = 9	IN group n = 7	p-valor
Clinical Global Impression-Improvement Scale (CGI-I)			
0 min (baseline)	4 (4.0, 5.0)	4 (3.0, 4.5)	1.0
10 min	0 (0.0, 1.5)	2 (2.0, 3.0)	0.041*
20 min	2 (1.0, 2.0)	3 (2.0, 4.0)	0.106
30 min	2 (1.5, 3.0)	3 (2.0, 4.0)	0.315
60 min	2 (2.0, 3.0)	3 (1.0, 4.0)	1.0
SAFETY			
	mean (SD)		
Heart rate (beats/min)			
0 min (baseline)	70 (11.0)	73 (27.8)	0.094
10 min	-0.5 (10.3)	0.0 (7.1)	0.921
20 min	-2.5 (9.5)	3.3 (7.3)	0.236
30 min	-1.7 (9.5)	2.7 (10.1)	0.418
60 min	-1.2 (16.1)	3.7 (5.6)	0.491

Blood pressure (mmHg)	Systolic	Diastolic	Systolic	Diastolic	Syst	Diast
0 min (baseline)	116.8 (12.5)	73.1 (9.3)	117.2 (11.3)	72.2 (7.0)	0.953	0.823
10 min	-0.1 (10.5)	-1.0 (6.2)	2.0 (5.3)	-4.2 (4.8)	0.662	0.320
20 min	4.4 (7.5)	-1.7 (3.2)	-1.8 (8.0)	-0.2 (6.0)	0.144	0.535
30 min	4.1 (11.5)	-0.2 (13.1)	3.5 (5.7)	0.3 (3.1)	0.906	0.984
60 min	1.4 (11.8)	-4.9 (8.8)	0.5 (3.3)	-0.5 (5.3)	0.854	0.297

ECG *QTc (mm/s)*			
Baseline	385 (27.8)	385 (27.8)	
Post-treatment change	-6.5 (-49.7; 3)	-19 (-48; 1)	0.463

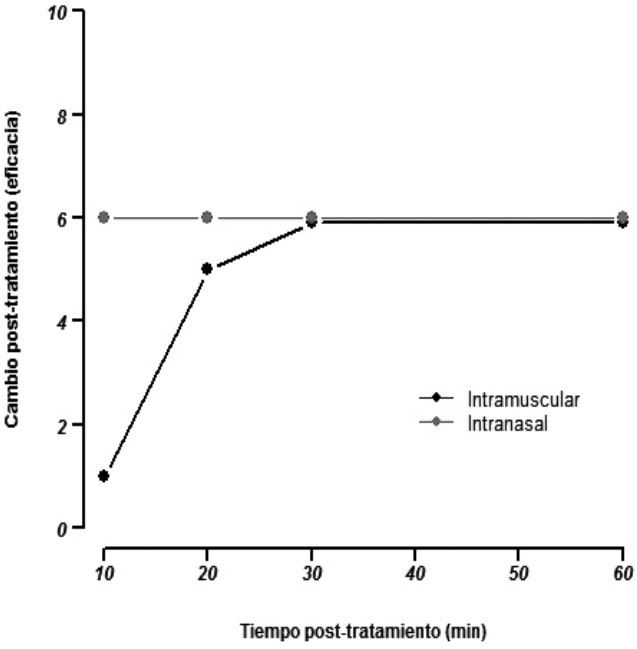
IM: Intramuscular group; IN: Intranasal Group; PANSS-EC: Positive and Negative Symptom Scale-Excited Component; CGI-I: Global Impression Scale-Improvement scale

Table 2 PANSS-EC and CGI-I scores for patients with psychomotor agitation

PANSS-EC		Excitement	Hostility	Tension	Uncooperativeness	Poor impulse control	Excited Component	CGI
		Median (25th, 75th percentiles)						
Baseline	IM	4 (3,0; 4,5)	3 (2,5; 3,5)	4 (4,0; 4,5)	3 (3,0; 3,5)	4 (2,0; 4,5)	17 (15,5; 20,5)	4 (3,0; 4,5)
	N	4 (4,0; 5,0)	4 (3,0; 4,0)	4 (4,0; 4,0)	3 (2,0; 4,0)	3 (3,0; 4,0)	17 (16,0; 22,0)	4 (4,0; 5,0)
10 min	IM	4 (2,5; 4,0)	3 (2,0; 3,0)	4 (2,5; 4,0)	2 (2,0; 3,5)	3 (2,0; 3,5)	16 (11,0; 18,0)	4 (2,0; 4,0)
	IN	3 (2,0; 3,0)	2 (2,0; 3,0)	3 (2,0; 4,0)	2 (2,0; 3,0)	3 (2,0; 3,0)	13 (10,0; 15,0)	2 (1,0; 3,0)
20 min	IM	3 (2,0; 3,0)	2 (2,0; 3,0)	3 (2,0; 4,0)	2 (2,0; 2,5)	2 (2,0; 3,5)	12 (10,0; 16,0)	2 (1,0; 3,0)
	IN	2 (2,0; 3,0)	2 (2,0; 2,0)	2 (2,0; 2,0)	2 (2,0; 2,0)	2 (2,0; 2,0)	10 (10,0; 11,0)	1 (1,0; 2,0)
30 min	IM	2 (2,0; 3,5)	2 (2,0; 3,0)	3 (2,0; 3,5)	2 (2,0; 3,0)	2 (2,0; 3,0)	10 (10,0; 16,0)	2 (1,0; 3,0)
	IN	2 (2,0; 3,0)	2 (2,0; 3,0)	2 (2,0; 3,0)	2 (2,0; 2,0)	2 (2,0; 2,0)	10 (10,0; 13,0)	1 (1,0; 1,0)
60 min	IM	3 (2,0; 3,0)	2 (2,0; 3,0)	3 (2,0; 3,0)	2 (2,0; 2,0)	2 (2,0; 2,0)	11 (10,0; 12,5)	1 (1,0; 2,0)
	IN	2 (2,0; 3,0)	2 (2,0; 2,0)	2 (2,0; 4,0)	2 (2,0; 2,0)	2 (2,0; 3,0)	10 (10,0; 15,0)	1 (1,0; 3,0)

IM: Intramuscular group; IN: Intranasal Group; PANSS-EC: Positive and Negative Symptom Scale-Excited Component; Excited component of the PANSS-EC: excitation + hostility + motor tension + lack of cooperation + poor impulse control; CGI-I: Global Impression Scale-Improvement scale

groups. Although this was greater for the IN route than the IM route, the difference was not statistically significant. No other side effects or excessive sedation was recorded.



PANSS-EC (Positive and Negative Syndrome Scale-Excited Component)

Figure 1 Haloperidol treatment Efficacy: IM and IN groups measured with the PANSS-EC Scale-Excited Component

DISCUSSION

The samples were randomised in this pilot clinical study into two parallel treatment arms (haloperidol IN vs. IM) in patients diagnosed with schizophrenia and schizoaffective disorder with mild-moderate psychomotor agitation admitted to an acute unit. IN administration of haloperidol was easy, non-invasive, inexpensive and safer for patients and healthcare personnel. It also showed faster sedation onset compared to the IM route.

Our study detected early signs of agitation and provided rapid intervention; calming the patient without sedating him excessively, which was a primary objective of their pharmacological management[1]. A study of the pharmacokinetics of haloperidol by Miller et al.[5] showed the IN route reached a maximum concentration in a shorter time. Our study was in agreement with this, finding an onset time of 10 minutes after administration for the haloperidol to take effect.

Regarding safety, electrocardiographic changes were detected in the post-treatment QTc, which were greater for the IN rather than the IM route; although not statistically significant or pathological in either case. As specified in the Summary of Product Characteristics (SmPC)[11], injectable haloperidol is indicated for IM administration only and has never been approved for IV. However, IV administration is quick and effective in controlling delirium and severe agitation in hospitalised critical patients, and is routinely used as if it were included in the SmPC. In 2007, the Food and Drug Administration (FDA) issued a safety warning regarding the indication of electrocardiogram monitoring in patients treated with intravenous haloperidol due to the potential risk of

prolonging QTc or torsades de pointes[12]. Over the years there has been concern about these cardiac side effects in published cases. However, updated scientific information[13] suggests a favourable safety profile for the drug administered by this route: in most prospective studies, IV haloperidol caused no greater QT prolongation than placebo, and the proportion of these severe cardiac arrhythmias was low. Special monitoring is recommended in the population at risk (patients who are critical or with concomitant cardiac pathology or who use other drugs that prolong the QT). An increased risk of prolonged QTc alterations has not been associated with IV administration of haloperidol at a maximum dose of 20 mg/day, and any risk is no higher than with other antipsychotics[13].

The IN route is not included in the SmPC and no cardiac complications have been reported with doses of 2.5 mg[5]. The results of this preliminary study and current scientific evidence[13] suggest haloperidol IN may be an alternative treatment for agitated patients in a hospital situation, after studying the risk factors and dose on a case-by-case basis. However, the safety and efficacy of the IN haloperidol should be confirmed with future studies.

The biggest limitation of the study is the small sample size; however, its homogeneity and randomisation into two parallel haloperidol administration arms compensate for this.

CONCLUSIONS

IN administration of 5 mg haloperidol is a non-invasive, rapid and effective alternative for the reduction of mild-moderate agitation in patients with schizophrenia and schizoaffective disorder admitted to an acute unit. The drug was well tolerated; however, caution is required in its administration due to the potential risk of side effects. The safety and efficacy of IN haloperidol could be confirmed by increasing the sample size in other studies.

Conflict of interests. None.

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