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Farmacia Hospitalaria
ISSN: 1130-6343
ISSN: 2171-8695
Grupo Aula Médica

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Farmacia Hospitalaria, vol. 41, no. 5, 2017
Grupo Aula Médica
Available in: http://www.redalyc.org/articulo.oa?id=365962297007
DOI: 10.7399/fh.10778

ORIGINAL BREVE

Polypharmacy and potential drug-drug interactions in an HIV-infected elderly population

Polifarmacia e interacciones farmacológicas potenciales en una población envejecida con infección por el VIH

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Farmacia Hospitalaria, vol. 41, no. 5, 2017

Grupo Aula Médica

Received: 27 February 2017
Accepted: 01 May 2017

DOI: 10.7399/fh.10778

Abstract

Objective: Comorbidities associated with the ageing of the HIV+ population may require chronic treatment. Our aim is to determine the degree of polypharmacy and the number of potential drug-drug interactions, as well as the relationship between both variables in a HIV-infected population over the age of 65.

Methods: Descriptive transversal study targeting HIV+ patients aged ≥65, attended in a Spanish hospital in 2014. The prevalence of polypharmacy (≥5 drugs) and potential drug-drug interactions were assessed, and also risk factors associated with such.

Results: 265 subjects aged ≥65 years were identified, 197 of whom were on antiretroviral treatment and had data about their electronic prescription. 93% were polymedicated. The patients whose antiretroviral treatment included a non -nucleoside reverse transcriptase inhibitor (NNRTI) demonstrated a fourfold probability of being polymedicated. 65% of the patients showed at least one potential drug-drug interaction and 6.6% a severe potential drug-drug interaction. The risk of interaction was significantly associated with the number of prescribed drugs (incidence rate ratio per prescribed drug, CI 95%: 1.18 (1.14;1.22; p<0.0001) and with the use of protease inhibitors (PI) (incidence rate ratio, CI 95%: 1.65 (1.28;2.11; p=0.0001)).

Conclusion: Polypharmacy has a high prevalence and is more common in patients treated with NNRTI. The number of potential drug-drug interactions increase with the number of prescribed drugs and is higher in those patients on PI.

KEYWORDS: Aged++ Drug interactions++ HIV infection++ Polypharmacy.

Resumen

Objetivo: Las comorbilidades asociadas al envejecimiento de la población VIH+ pueden requerir tratamientos crónicos. Nuestro objetivo es determinar el grado de polifarmacia

y el número de interacciones farmacológicas potenciales, así como la relación entre ambas variables en un grupo de población VIH+ mayor de 65 años.

Métodos: Estudio descriptivo transversal en pacientes VIH+≥65 años atendidos en un hospital español en 2014. Se evaluó la prevalencia de polimedicación (≥5 fármacos) y se analizaron las interacciones farmacológicas potenciales y los factores de riesgo asociados a ellas.

Resultados: Se identificaron 265 sujetos ≥65 años, de los cuales 197 recibían tratamiento antirretroviral y tenían datos en la receta electrónica. El 93% estaban polimedicados. Los pacientes cuyo tratamiento antirretroviral incluía un inhibidor de la transcriptasa inversa no nucleósido (ITINN) presentaban una probabilidad cuatro veces mayor de estar polimedicados. El 65% de los pacientes presentó al menos una interacción potencial y el 6,6% una interacción potencial grave. El riesgo de interacciones se asoció significativamente al número de fármacos prescritos (razón de tasas de incidencia por fármaco prescrito con IC 95%: 1,18 (1,14;1,22; p<0.0001)) y a los inhibidores de la proteasa (IP) (razón de tasas de incidencia IC 95%: 1,65 (1,28;2,11; p=0,0001)).

Conclusión: La prevalencia de la polifarmacia es muy alta y más frecuente en los pacientes tratados con ITINN. El número de interacciones farmacológicas potenciales aumenta con el número de fármacos prescritos y es mayor en los pacientes tratados con IP

PALABRAS CLAVE: Infección VIH, Interacciones farmacológicas, Mayores, Polifarmacia.

Introduction

Although it is currently not possible to eradicate HIV infection, high activity antiretroviral therapy (ART) has made it possible to reduce mortality and turn it into a chronic disease.

Life expectancy for the general population in Spain is increasingly longer, being in 2014 of 85.6 years for women and 80.1 years for men. There is a progressively growing number of people over the age of 65 and a parallel increase in comorbidity that require chronic treatment. The same is true for the population infected by HIV[1].

Polypharmacy or polymedication is associated with greater complexity in the management of therapeutic treatment and with increased risk of adverse events and drug-drug interactions, mismedication, reduced adherence to treatment and falls[2]. It is also related to an increase in hospitalisation and mortality[3]. Taking into account that standard ART is based on the simultaneous administration of 3 different drugs[4], polypharmacy is common[1]. Nevertheless, there is little data on the population infected by HIV over the age of 65.

Therefore, the aim of this study is to determine the level of polypharmacy and the number of potential drug-drug interactions, as well as the relationship between both variables, in a group of patients infected by HIV over the age of 65 belonging to a large cohort of HIV+ patients.

Methods

Descriptive cross-sectional study conducted at a tertiary Spanish university hospital with over 4,500 HIV-infected patients under active follow-up. It included all patients ≥65 years of age who received antiretroviral treatment and had a chronic medication record in the

CatSalut's Electronic Prescription System (SIRE) in November 2014. Transfers and exitus were excluded. Polypharmacy was defined as taking 5 or more drugs[2]. Clinical variables (time since HIV diagnosis, HIV transmission mode, acquired immune deficiency syndrome (AIDS) diagnosis, viral load, CD4 lymphocyte count and hepatitis C virus serology) and demographics (age and gender) were evaluated, as well as the ART and concomitant medication, which was classified according to the Anatomical Therapeutic Chemical (ATC) Classification System.

A screening for potential drug-drug interactions was conducted with the HIV Interactions database from the Hospital Clínic de Barcelona[5] and the HIV Drug Interactions database from the University of Liverpool[6]. Later , they were classified according to their relevance, defining them as moderate if they required monitoring/dosage adjustment and severe if their concomitant use was contraindicated/ not recommended[5,6]. They were also classified according to whether the interaction type was pharmacokinetic or pharmacodynamic, and whether it affected the ART or the chronic medication.

The study was not assessed by a clinical research ethics board, as it was not deemed to affect the care given to the patients at the hospital.

The statistical analysis was conducted with version 13 of the Stata program. The categorical variables were expressed with absolute frequencies and percentages. The continuous variables with average and standard deviation (SD) or median and interquartile range (IQR). To evaluate possible differences between the polymedicated and non-polymedicated groups of patients, the Chi-squared test or the Fisher's exact test was used for qualitative variables and the Student's t-testor Mann-Whitney U test for quantitative variables. A logistical regression was conducted to identify factors (demographic, clinical and ART) associated with polymedication and a Poisson regression to assess variables associated with the incidence of interactions. Bilateral values of $p<0.05$ were considered statistically significant.

Results

In our cohort of HIV+ patients, we identified 6% (n=265) of subjects ≥65 years. Sixty-eight patients were excluded due to transfer to other regions (n=2), exitus (n=7), lack of data in SIRE (n=58) or because of not receiving antiretroviral therapy (n=1). The remaining 197 patients were included in the study. 80% were men and the average age was 71 years. The characteristics of the population are summarised in Table 1. The statistical analysis showed no significant differences in the demographic and clinical variables between polymedicated and non-polymedicated patients.

Table 1
Characteristics of the HIV-positive population ≥ 65 years

Variable	Global	Men	Women
Patients, *n (%)*	197	157 (79.7)	40 (20.3)
Age, *Median* ± SD	71.2±5.4	71.1±5.4	71.5±5.4
Transmission mode, *n (%)*			
– HMSX and non-IDU	93 (47.2)	91 (58.0)	2 (5.0)
– HTSX and non-IDU	73 (37.1)	40 (25.5)	33 (82.5)
– Unknown	17 (8.6)	14 (8.9)	3 (7.5)
– IDU (unspecified sexual orientation)	2 (1.0)	1 (0.6)	1 (2.5)
– HMSX and IDU	2 (1.0)	2 (1.3)	0 (0)
– Bisexual and non-IDU	8 (4.1)	8 (5.1)	0 (0)
– Transfusion (unrelated to haemophilia)	2 (1.0)	1 (0.6)	1 (2.5)
Time since HIV diagnosis, *Median in years* ± SD	16.1±6.4	16.1±6.7	16.4±5.1
AIDS diagnosis, *n (%)*	66 (33.5)	58 (36.9)	8 (20.0)
Time since AIDS diagnosis, *Median in years* ± SD	15.9±5.9	16.1±5.9	14.9±6.1
Indetectable viral load (<37 copies/mL), n (%)	189 (95.9)	150 (95.5)	39 (97.5)
CD4 lymphocyte count *(cell/mm³), Median* ± SD	550.1±255.2	528.5±247.9	635.1±268.9
VHC+ serology, *n (%)*	17 (8.6)	11 (7.0)	6 (15.0)
Number of drugs belonging to the chronic treatment, *Average* ± SD	5.6±3.0	5.5±3.0	5.8±3.2

AIDS: Acquired Immune Deficiency Syndrome; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HMSX: Homosexual; HTSX: Heterosexual; IDU: Intravenous Drug User; SD: standard deviation.

One hundred and eighty-three patients (93%) were polymedicated. The average ± SD of drugs associated with the ART was 5.6 ± 3.0 and most of them were used to treat diseases associated with the cardiovascular system, metabolism and the central nervous system.

57% of the patients received 2 nucleoside reverse-transcriptase inhibitors (NRTI) and 1 non-nucleoside reverse-transcriptase inhibitors (NNRTI), 33% 2 NRTI and 1 protease inhibitors (PI), 20% 2 NRTI with one integrase inhibitor (INI). A single patient could receive drugs from several of these families. The remaining 1% used other less common combinations. In the logistical regression model, patients whose ART included a NNRTI had a significantly higher probability of being polymedicated (OR adjusted for age with CI 95%: 4.29 (1.27;14.52); p=0.0193).

65% of the patients had at least one potential drug-drug interaction, and 6.6% had a severe potential interaction. 33% had two or more potential interactions. A total of 259 potential interactions were detected, of which 92% were pharmacokinetic and the rest (8%) pharmacodynamic. 82% of the interactions affected only the drug belonging to the chronic medication, 8% affected only the ART and 10% affected both. Of the interactions that affected the drug from the chronic medication, 56% compromised the efficacy of the treatment, while 42% could cause toxicity. The consequence of the interaction is unknown in 4 cases, although they probably could have affected efficacy or toxicity. Amongst the interactions that affected the ART, 45% could reduce efficacy and 55% could increase toxicity.

Interactions were observed in 72% of the patients treated with PIs, in 68% of the patients with NNRTIs and in 51% of those treated with INIs. The number of interactions was significantly higher in patients treated

with PIs compared to the rest (incidence rate ratio with CI 95%: 1.65 (1.28;2.11); p=0.0001).

Also, a statistically significant association was observed between the number of prescribed drugs and the number of interactions (incidence rate ratio by prescribed drug with CI 95%: 1.18 (1.14;1.22); p<0.0001).

Figure 1 shows the prevalence of potential drug-drug interactions based on the number of prescribed drugs and antiretroviral treatment.

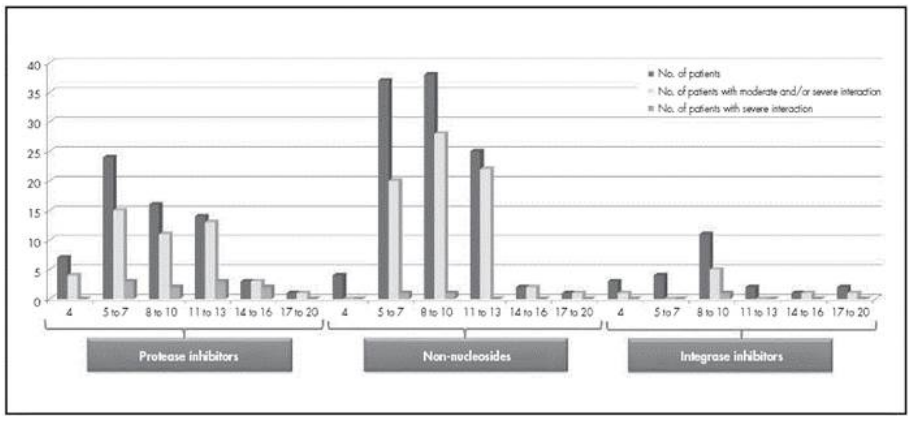

Figure 1

Prevalence of potential drug-drug interactions based on the number of prescribed drugs and antiretroviral treatment. Based on the type of antiretroviral treatment, you can see, on the x-axis, the total number of drugs (including antiretroviral treatment (combination of 3 drugs) and the treatment belonging to chronic medication) and, on the y-axis: the total number of patients receiving it, number of patients with at least a moderate potential drug-drug interaction and number of patients with a severe potential drug-drug interaction.

Regarding associated chronic treatment, the risk of interaction was significantly higher in patients that received drugs to treat pathologies of the alimentary tract and metabolism (ATC: group A; incidence rate ratio with CI 95%: 1.99 (1.44;2.75, p<0.0001)), nervous system (ATC: group N; incidence rate ratio with CI 95%: 1.72 (1.32;2.23, p<0.0001)), genito urinary system and sex hormones (ATC: group G; incidence rate ratio with CI 95%: 1.67 (1.28;2.18, p<0.0001)), musculo-skeletal system (ATC: group M; incidence rate ratio with CI 95%: 1.61 (1.20;2.15, p<0.0015)), cardiovascular system (ATC: group C; incidence rate ratio with CI 95%: 1.57 (1.12;2.21, p=0.0083)) and of the blood and blood forming organs (ATC: group B; incidence rate ratio with CI 95%: 1.29 (1.01;1.65, p=0.0413)).

Discussion

The results of our study confirm that polymedication is almost universal in patients over the age of 65. Marzolini et al. agree that polypharmacy is common in the population of elderly HIV-infected adults[1]. The prevalence of polymedication in our cohort (93%) is greater than described by Guthrie et al. in the general population in Scotland[7]. These authors found that, in 2010, approximately 40% of patients

over the age of 65 took ≥ 5 drugs and 10% ≥10 drugs. This major difference in prevalence of polymedication may possibly be due to the fact that the appearance of comorbidities associated with age occurs 10 years sooner in the HIV+ population than in the general population and that ART itself includes 3 drugs[8]. As a consequence, there is an earlier use of medication for the treatment of these comorbidities in the HIV-positive population. The types of drugs most commonly used in our cohort of patients coincides with previous studies[1,2,9], with a greater use of statins, antihypertensives, antacids, vitamins, antidiabetics, antidepressant, antipsychotics and androgens.

As regards the demographic characteristics, as in previous studies[1,2], in our study's population there was a predominance of male patients and the primary mode of HIV transmission was men who had sex with men. In this age group, no differences were observed compared to the rest of our cohort.

Approximately two-thirds of our patients had some potential drug-drug interaction, and 6.6% had a severe potential interaction. Most were pharmacokinetic and were related to non-antiretroviral drugs, as in the studies of Marzolini et al.[1] and Greene et al.[2].

The results show that the probability of drug-drug interaction increases with the number of prescribed drugs, illustrating one of the consequences of polypharmacy. Besides, the greater prevalence of interactions in patients treated with PIs suggests that the use of INIs or NNRTIs would be a safer option in polymedicated patients. Thus, the differences in the ART used in the polymedicated and non-polymedicated groups (lower use of PIs and greater use of NNRTIs in polymedicated patients) can be explained, in part, by the intent to avoid drug-drug interactions.

Our results, similar to those observed in other studies[8,10], indicate that special attention should be paid in patients treated with PIs. A high risk of interactions is also estimated in patients treated with cobicistat, although at the time of the study, only two patients received it, as it was just starting to be used as part of the ART. Nor should we forget the interactions between chronic non-antiretroviral medication drugs, which have not been assessed in our study.

One limitation of the study is that we are not aware of the current situation of the 58 patients with no data in the SIRE; that is, we do not actually know whether they did not receive other drugs or their treatmentwas not recorded. However, we must highlight that the study was conducted in one of the largest cohorts of patients infected with HIV in our country.

In conclusion, our results provide evidence that the prevalence of polypharmacy in elderly HIV+ patients is very high and more frequent in patients treated with NNRTIs. The number of potential drug-drug interactions increases with the number of prescribed drugs and is greater in patients treated with PIs. These data support the need to change the care given to patients with HIV[2], periodically reviewing the medication and incorporating the guidelines for drug usage in the elderly, which

should be adapted to the population infected with HIV[10]. Given its complexity, a multidisciplinary approach is required.

Contribution to Scientific Literature

Our study was conducted in one of the largest cohorts of patients infected by HIV in our country. In particular, it analyses a group of patients that will be increasingly relevant in clinical practice because advances in the pharmacological approach for the management of the disease have enabled the HIV-positive population to age.

Our results provide information on the prevalence of polypharmacy in said subjects, illustrating that it is a nearly universal situation in patients over the age of 65. Potential drug-drug interactions derived from polypharmacy were also analyzed, contributing data on its prevalence and clinical relevance.

Finally, we identify the drug groups belonging to chronic medication with a high risk of drug-drug interaction, as well as the antiretroviral classes with high risk.

There is little data on elderly patients infected by HIV over 65 years, so our results may be of interest in clinical practice. We bring to light the need to change the care given to HIV patients, which should focus on a multidiscipline approach due to its high complexity. Periodic reviews of the medication should be promoted, as well as the inclusion of drug usage guidelines for the elderly adapted to the HIV-positive population.

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