Original Paper

Patients in chronic prednisone use in a Brazilian municipality: are potential adverse events being monitored?

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Abstract

Introduction: chronic use of corticosteroids can trigger several adverse effects with changes in glycemic, lipid, liver enzymes and electrolyte levels. Therefore, the the aim of the present study was to analyze if the patients on chronic prednisone use from the Brazilian Public Health System (PHS) in a Midwestern municipality of the state of Minas Gerais were monitored for their adverse effects through laboratory tests. **Methods**: a longitudinal descriptive study was carried out with retrospective data from patients attended by the PHS of this city, and who have used prednisone chronically for three consecutive years, from 2014 to 2016. The frequency of patients who underwent tests to monitor adverse events from the chronic use of prednisone was verified through electronic records in the Integrated Health System (IHS). The following types of tests were analyzed: total serum calcium, urine calcium (24-hour urine), serum phosphate, alkaline phosphatase, fasting glucose, sodium (Na+), potassium (K+), and lipidogram (triglycerides, LDL, VLDL, HDL, and total cholesterol). **Results**: it was observed that fasting glucose and lipidogram were the tests that presented the highest number of annual records. However, for the other examined parameters, which are essential for the follow-up of patients in chronic use of corticosteroids, the non-monitoring index is greater than 80 %. **Conclusions**: the results revealed an inadequate frequency of laboratory monitoring of patients in chronic prednisone use, indicating the occurrence of prescriptions without the monitoring of possible adverse effects, which may constitute safety problems for patients.

Keywords: Prednisone; Risk management; Drug-related side effects and adverse reactions.

Pacientes em uso crônico de prednisona em um munícipio brasileiro: os possíveis eventos adversos estão sendo monitorados?

Resumo

Introdução: o uso crônico de medicamentos corticoides pode desencadear a ocorrência de vários efeitos adversos com alterações nos níveis glicêmicos, lipídicos, enzimas hepáticas e eletrólitos. Portanto, o objetivo deste estudo foi verificar se os pacientes em uso crônico de prednisona do Sistema Único de Saúde (SUS) em um município do Centro-Oeste do Estado de Minas Gerais foram monitorados com relação aos seus efeitos adversos através de exames laboratoriais. **Métodos**: realizou-se um estudo descritivo de caráter longitudinal com dados retrospectivos de pacientes atendidos pelo SUS deste município e que fizeram uso crônico de prednisona por três anos consecutivos, de 2014 a 2016. A frequência de pacientes que realizaram exames para monitorização de eventos adversos ao uso crônico de prednisona foi verificada por meio dos registros eletrônicos no Sistema Integrado de Saúde (SIS). Foram analisados os seguintes exames: Cálcio total sérico, Cálcio urinário (urina 24hs), Fosfato sérico, Fosfatase alcalina, Glicose de jejum, Sódio (Na+), Potássio (K+), e Lipidograma (Triglicérides, LDL, VLDL, HDL e colesterol total). **Resultados**: observou-se que glicemia de jejum e o lipidograma foram os exames que mais apresentaram registro anual de monitorização. Contudo, para os demais parâmetros analisados, essenciais ao acompanhamento de pacientes em uso crônico de corticoides, o índice de não monitorização é superior a 80%. **Conclusões**: os resultados evidenciam inadequada frequência de monitorização laboratorial dos pacientes em uso crônico de prednisona, indicando a ocorrência de prescrições sem o acompanhamento dos possíveis efeitos adversos, o que pode constituir em problemas de segurança para os pacientes.

Palavras-chave: Prednisona; Gestão de riscos; Efeitos colaterais e reações adversas relacionados a medicamentos.

Submitted: 01/10/18
Rebmitted: 28/12/19
Accepted: 31/12/19
Blind reviewers

DOI: 10.30968/rbfhss.2019.104.0343
ISSN online: 2316-7750

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Introduction

Corticosteroids are drugs widely used in clinical practice and commonly prescribed for the treatment of diseases of allergic, inflammatory, or autoimmune origin. They mimic the effects of the endogenous hormonal steroids cortisol (glucocorticoid) and aldosterone (mineralocorticoid) produced by the adrenal cortex.[1] Although the efficacy of these drugs is widely recognized, their use in high doses, as well as their rapid suspension after a long period of use, can result in the occurrence of important adverse events.[2]

Some of the main adverse effects caused by chronic use of corticosteroids are metabolic changes such as increased insulin resistance, increased plasma glucose, changes in body fat distribution, and altered lipid metabolism; electrolyte imbalance (increase in sodium (Na^+) reabsorption and excretion of potassium (K^+), acid (H^+), and calcium ($Ca2^+$) by the kidneys); weight gain; ocular changes; decreased muscle and bone mass; and the development of osteoporosis.[2,3]

The wide variety of systemic adverse events associated with this pharmacological class is caused by its mineralocorticoid and glucocorticoid activities, since they interfere in the general metabolism of the organism. The former affects the hydroelectrolytic balance, with a specific function in the regulation of water in the body and in the control of the excretion and reabsorption of sodium in the kidneys. The latter acts on the metabolism of carbohydrates and proteins, antagonizing peripheral actions of insulin and triggering increased hepatic gluconeogenesis, with diabetogenic potential.[4,5] The ability of glucocorticoids to influence the metabolism of lipoproteins raising serum levels of total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), and triglycerides is also known.[6,7]

Among the side effects caused by glucocorticoids, the development of osteoporosis is one of the most serious. Their chronic use produces changes in the physiological process of bone remodeling, leading to a decrease in bone mineral mass and a consequent increase in the incidence of fractures.[8] Thus, several laboratory tests are recommended to monitor and evaluate osteoporosis induced by corticosteroids. Serum $Ca2^+$ dosage, as well as in 24-hour urine calcium dosage, blood phosphate, and alkaline phosphatase are some of the most important. The possible pathophysiological mechanisms associated with the occurrence of osteoporosis related to the use of corticosteroids justify the indication of laboratory tests that can aid in the diagnosis and monitoring of the disease.[9]

Thus, we can realize the need for clinical and laboratory monitoring of patients who use chronic corticosteroids. The previously mentioned tests (Serum $Ca2^+$, 24-hour urine calcium dosage, blood phosphate, and alkaline phosphatase) together with fasting glucose, Na^+, K^+, and lipidogram can help identify possible laboratory alterations which allow control, prevention, and treatment measures based on the possible alterations, to be implemented in clinical protocols and in the management of health services. The aim of the present study was to analyze if the patients on chronic prednisone use from the Brazilian Public Health System (PHS) in a midwestern municipality of the state of Minas Gerais were monitored for their adverse effects through laboratory tests.

Methods

This is a retrospective longitudinal descriptive study that included patients attending PHS pharmacies that dispense drugs from the basic component of Pharmaceutical Assistance in a midwestern municipality of Minas Gerais state, Brazil. This city currently has an estimated population of 234,937 inhabitants and 12 health regions, where there are 14 conventional health centers (CHS), 20 Family Health Strategy (FHS) units, and five pharmacies which dispense medication from the basic component of Pharmaceutical Assistance.[10]

To identify and recruit all patients in chronic prednisone use, a survey was carried out by means of electronic registration of the dispensations of this drug performed from 2014 to 2016. Patients 18 years of age and over who used prednisone for at least 90 days were included. The dispensation of medication and the results of all laboratory tests are recorded in an electronic health system of the municipality known as the Integrated Health System (IHS).

The frequency of patients who underwent tests to monitor adverse events for the chronic use of prednisone was verified through electronic records in the IHS. The following tests were analyzed: total serum calcium, urine calcium (24-hour urine), serum phosphate, alkaline phosphatase, fasting glucose, sodium (Na^+), potassium (K^+), and lipidogram (triglycerides, LDL, VLDL, HDL, and total cholesterol). Tests which might have been performed in private laboratories were not evaluated.

Descriptive statistics was performed with categorical variables reported in absolute and relative frequencies. The McNemar χ^2 test with 5 % significance was performed to compare the proportions of patients who underwent laboratory test at 3 years and those who didn't by sex and age. In this step, the R program, version 4.4.2 was used.

The work was approved by the Human Research Ethics Committee of the Federal University of São João del-Rei, Dona Lindu Center-west Campus, located in Minas Gerais on Juny 19, 2015 (CAAE approval: 45858315.0.0000.5545).

Results

A total of 168 adult and elderly patients who had access to prednisone in 2014 were identified. Of these, 37 were excluded because they did not present consecutive use in the three-year period established for data analysis in the present study. Thus, 131 participants remained. Women prevailed with 72.5 % (n=95) and the mean age in the sample was 56 years, with a standard deviation (SD)=9.3. Table 1 shows the sociodemographic characteristics and monitoring of these patients. The differences between sex and age were not statistically significant.

Regarding the frequency with which the patients performed the laboratory tests to monitor adverse effects, it was observed that fasting glucose and lipid profile (routine tests) were the tests that presented the highest number of annual records, but approximately one third of the patients did not perform these tests in any of the three examined years. Analysis of the specific tests (total serum calcium, 24-hour urine calcium, serum phosphate, alkaline phosphatase, sodium, and potassium) revealed that the non-monitoring index was higher than 80 % of the patients analyzed. It was also observed that the number of routine tests presented a marked decrease year by year and the number of specific tests showed a significant variation (Table 2).

Table 1. Sociodemographic characteristics and monitoring of patients in chronic use of prednisone in a Midwestern municipality of Minas Gerais state (n=131).

Sociodemographic characteristic	Total patients % (n)	Patients who had some laboratory tests in all the three years % (n)	Patients who did not undergo laboratory tests in any year % (n)	P value
Sex				
Female	72.5 (95)	23.2(22)	26.3(25)	0,073
Male	27.5 (36)	11.1(4)	44.4(16)	
Age				
≤ 40 years	12.2 (16)	0(0)	31.3(5)	0,339
Between 41 and 59 years	45.8(60)	23.3(14)	26.7(16)	
≥ 60 years	42.0 (55)	20(11)	36.4(20)	

Table 2. Frequency of adults and elderly of a midwestern municipality of Minas Gerais state in chronic use of prednisone through the PHS who underwent laboratory test from 2014 to 2016 (n=131).

Test	2014 % (n)	2015 % (n)	2016 % (n)	Patients who did not undergo laboratory tests in any year % (n)
Fasting glucose	53.4 (70)	47.3 (62)	43.5 (57)	29.0 (38)
Triglycerides	44.2 (58)	41.0 (54)	35.8 (47)	35.1 (46)
LDL	38.9 (51)	35.8 (47)	27.4 (36)	35.8 (47)
VLDL	38.9 (51)	35.8 (47)	27.4 (36)	39.6 (52)
HDL	39.6 (52)	36.6 (48)	30.5 (40)	38.9 (51)
Total cholesterol	43.5 (57)	41.2 (54)	35.8 (47)	33.5 (44)
Sodium	1.5 (2)	6.8 (9)	8.3 (11)	85.4 (112)
Potassium	5.3 (7)	11.4 (15)	9.1 (12)	82.4 (108)
Total serum calcium	3.0 (4)	6.1 (8)	2.2 (3)	91.6 (120)
Urine calcium	0.0 (0)	1.5 (2)	0.0 (0)	98.4 (129)
Serum phosphate	2.2 (3)	1.5 (2)	0.76 (1)	96.1 (126)
Alkaline phosphatase	2.2 (3)	6.1 (8)	3.0 (4)	92.3 (121)

Discussion

The results found in the present study show a significant number of patients in chronic use of corticosteroids who do not present a record of performing laboratory tests at the PHS during the analyzed period. These findings demonstrate the need to raise awareness of healthcare professionals from different specialties of the importance of guiding patients on the serious adverse events that chronic use of corticosteroids can trigger.

In this context it is important to consider that, although the use of corticosteroids may offer several benefits to patients because of their anti-inflammatory and immunosuppressive properties, they can cause metabolic alterations that can lead to the development of diseases such as diabetes mellitus, hypertension, dyslipidemia, and osteoporosis.[11,12] Therefore, monitoring these patients becomes imperative.

In this study, 72.5 % (n=95) of the patients were women, and the sample had a mean age of 56 years (SD=9.3). Considering that corticosteroids are used to treat rheumatoid arthritis, which affects twice as many women as men and has an incidence that increases with age, the characteristics of the sample are consistent with the field literature.[13,14]

Patients in chronic use of systemic corticosteroids should be monitored frequently before, during, and after treatment as a means to detect the need for early interventions.[7] However, the results show a gap between this recommendation and the practice of monitoring, since a significant percentage of the users served by the PHS are not monitored, which makes preventive actions unfeasible.

Monitoring of patients undergoing intensive corticosteroid therapy is characterized by laboratory tests (fasting glucose, sodium, potassium, total cholesterol and fractions, and triglycerides). These tests should be performed one month after starting treatment and repeated every three to six months.[15] Therefore, this whole process is fundamental as a way of early diagnosis and follow-up of patients. In this sense it is important to emphasize that in the present study, fasting glucose and lipid profile stood out among the most frequently requested tests. This can be explained by the fact that these tests are considered routine in clinical practice. This fact, in addition to a lack of monitoring of parameters that are not considered part of clinical routine, suggests that monitoring potential adverse events associated with the use of prednisone still presents a gap in health services.

In this context, it is important to note that an Australian study identified that the cost associated with adverse effects related to prolonged use of oral corticosteroids in the treatment for severe asthma is US$ 598.32 per patient/year.[16] Therefore, adverse effects associated with the chronic use of corticosteroids, in addition to clinical worsening, have a significant financial impact for both patients and public health. Thus, monitoring these patients goes beyond the clinical issues of identifying adverse effects, since they must also be implemented to optimize the use of public resources.

It is important to stress that the present study has some limitations. The high frequency of non-monitoring of patients through laboratory tests may have been overestimated as a consequence of lack of information on tests which may have been performed in the private health sector. On the other hand, it is important to emphasize that, among the contributions of the investigation, the longitudinal design of the study allows for the identification of potential failures in the monitoring of patients assisted by the PHS. To our knowledge, this is the first Brazilian study to evaluate these parameters for this long period of time.

Conclusions

The results show an inadequate frequency of laboratory monitoring of the possible adverse events associated with the chronic use of prednisone. These patients should be carefully monitored because of the possibility of negative clinical and economic outcomes for patients and health services. Therefore, educational actions are necessary for health professionals as a way of guiding them to prevent, identify, and treat possible adverse events.

Funding source

None.

Authors' Contribution:

Bolina VMG- Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Drafting manuscript. Mendonça TS - Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Drafting manuscript. Pereira ML- Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Drafting manuscript. Domingueti, CP- Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Drafting manuscript. Rodrigues JPV – Conceptualization, Formal analysis, Methodology, Visualization, Drafting manuscript. Reis TM – Conceptualization, Formal analysis, Methodology, Visualization, Drafting manuscript. Baldoni AO - Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Drafting manuscript.

Conflict of interest

The authors declare that they have no conflict of interest in this paper.

Acknowledgements

We would like to thank the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* – Brazil (CAPES) – Finance code 001.

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