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Adverse drug reactions and medication adherence to oral antidiabetic drugs in patients: A longitudinal study

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Abstract

The World Health Organization (WHO) has indicated that treatment adherence in most patients with type 2 diabetes (T2D) is low and may be affected by the presence of adverse drug reactions (ADRs) associated with hypoglycemic pharmacotherapy The aim of this study was to analyze the relationship between the degree of pharmacotherapeutic adherence and the appearance of ADRs in people with T2D. A three-month prospective study was conducted, in which pharmacotherapeutic adherence was assessed using an indirect method, while ADRs were identified and characterized through active pharmacovigilance in outpatients at a public hospital in southern Mexico. Patients with T2D between 18 to 60 years, of both sexes, under pharmacological treatment with metformin and/or glyburide were included. The incidence and characteristics of ADRs, as well as the degree of pharmacotherapeutic adherence, were analyzed. Comparative analysis was carried out between adherent and non-adherent patients, evaluating the presence or absence of ADRs using the Chi-square test or Fisher's exact test. 92 patients were included, 106 ADRs were detected in 42 patients, the cumulative incidence was 45.65%. The proportion of ADRs among non-adherent patients was significantly higher than adherent patients (Chi-square test = 4.64; p = 0.031) and the Gastrointestinal disorders was the System Organ Class most affected (48.11%). Causality of the ADRs was mostly "probable" and severity "mild" category was the most frequent. These results provide objective evidence on the relationship between poor adherence and a higher prevalence of adverse drug reactions (ADRs) to oral hypoglycemic treatment using real-world data.

Keywords: Diabetes Mellitus; Adverse Drug Reactions; Treatment Adherence; Antidiabetic Drugs

1. Introduction

Diabetes is a chronic metabolic disease, triggered by hereditary, cultural or environmental factors, capable of generating changes in carbohydrate metabolism [1]. Type 2 diabetes (T2D) is the most prevalent type of diabetes worldwide and is mainly characterized by hyperglycemia caused by deficient secretion of insulin, tissue insulin resistance (IR), and an inadequate compensatory insulin secretory response [2, 3].

The aim of pharmacological treatment for T2D is to achieve glycemic control. According to clinical practice guidelines in Mexico, the initial treatment includes the use of antihyperglycemic drugs such as biguanides and sulfonylureas.

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However, these drugs can also cause adverse effects that affect the expected clinical outcomes [4]. According to the World Health Organization (WHO), and adverse drug reaction (ADR) is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function" [5]. Another crucial factor to achieve glycemic control in the management of T2D is patient adherence to their pharmacological treatment, which has been defined as "the degree to which a person follows pharmacological prescriptions as indicated" [6].

Previous reports have documented that ADR and lack of pharmacotherapeutic adherence negatively affect glycemic control [7]. However, in Mexico there are no studies that jointly evaluate these variables.

In order to investigate the possible association between the degree of pharmacotherapeutic adherence and the occurrence of ADRs in people with T2D, we carried out a prospective study. Pharmacotherapeutic adherence was evaluated using an indirect method, while ADRs were characterized using the active pharmacovigilance method.

2. Material and methods

2.1. Study design and population

A prospective study was carried out for three months in the Clinical Pharmacy department with outpatients of a public hospital in southern Mexico. Patients were monitored during the study period to measure the degree of pharmacotherapeutic adherence and to identify the presence of ADRs. Patients from the Yucatan Peninsula, with T2D, aged 18 to 60 years, of both sexes, under pharmacological treatment with metformin and/or glyburide were included. Pregnant women, patients with associated malignant condition and acute communicable diseases, with incomplete information in their medical records or who did not complete the follow-up period were excluded.

2.2. Patient data

Patient records were analyzed to collect age, sex, weight, height, body mass index (BMI), glucose levels, percentage of glycated hemoglobin (%A1c), duration of disease, prescribed medicines, and the dosage used. The registration was done electronically.

2.3. Pharmacotherapeutic adherence evaluation

Adherence to oral antihyperglycemic medication was measured using the 8-item Morisky Medication Adherence self-report questionnaire (MMAS-8). With the result obtained, patients were categorized into two groups of AFT according to the score obtained: non-adherent (<6 points) and adherent (6 to 8 points) [7].

2.4. ADR identification and evaluation

We used the definition of ADR according to the WHO [8]. The MedDRA® System Organ Class (SOC) was used to classify the system or organ affected by ADRs. ADR causality was assessed using the Naranjo algorithm [9]. This algorithm assigns a level of association between the ADR and the suspected drug, based on the score obtained in a questionnaire (maximum score: 13 points). The causality levels are: definitive (≥9 points), probable (5–8 points), possible (1–4 points), and doubtful (0 points).

Additionally, the ADRs were evaluated based on the criteria described in the Mexican Official standard NOM-220-SSA1-2016, Installation and operation of pharmacovigilance [10]. Severity was assigned as mild (signs and symptoms easy to tolerate, do not require treatment, do not prolong hospitalization), moderate (do not directly threaten the life of the patient, require pharmacological treatment, and may require discontinuation of treatment), severe (directly threatening the patient's life, prolonging hospitalization, can cause disability or disorders and malformations in the newborn) and fatal (directly or indirectly contribute to the death of the patient). Serious ADRs were considered those where "any clinical manifestation that occurs with the administration of any dose of a medication, including vaccines, and that: causes the death of the patient, endangers the patient's life at the moment it occurs, causes necessary to hospitalize or prolong the hospital stay, are the cause of disability or permanent or significant disability or are the cause of alterations or malformations in the newborn [10].

2.5. Statistical analysis

Descriptive statistics was used to summarize data. Student´s *t* test was used to compare mean where necessary. Comparative analysis between patient's non-adherent and adherent was performed by Chi-square test or Fisher´s exact test, as appropriate, for qualitative variables.

All results were considered to be statistically significant at $p < 0.05$. Data management and statistical analysis were carried out using Jamovi Statistics software 2.6.22 version.

2.6. Ethical implication

The study was carried out with prior approval from the hospital's Ethics and Research Committees. In addition, informed consent was obtained from all study participants and the confidentiality of the information collected was guaranteed at all times.

3. Results

A total of 92 patients with DT2 were included in the study, the women being the majority (n=49, 53.30%). The mean age was 45.20 ± 9.14 years. Table 1 shows the baseline characteristics of patients.

In the present study, all patients received oral hypoglycemic agents (metformin and/or glyburide). Metformin was the most common drug of choice in the study sample (66/92 patients; 71.7%). Of the 92 patients in the study, 35.87% were non-adherent, while 64.13% were adherent.

Table 1 Baseline clinical and pharmacological characteristics of patients in the study cohort

Characteristics	**Men**	**Woman**	**Total**	***P-value***
n (%)	43 (46.70%)	49 (53.30%)	92	-
Age (years), mean ± SD	43.7 ± 9.35	47.3 ± 7.08	45.20 ± 9.14	0.040*
Clinical characteristics, mean ± SD				
Duration of diabetes (years)	2.84 ± 4.50	3.66 ± 5.21	3.28 ± 4.88	0.421
BMI (kg/m^2)	34.00 ± 6.54	35.14 ± 6.98	34.6 ± 6.76	0.427
Glucose levels (mg/dL)	196.30 ±72.06	171.69 ± 79.71	183 ± 76.80	0.126
%A1c	9.22 ± 2.30	8.35 ± 2.51	8.76 ± 2.44	0.088
Antidiabetic drug n (%)				
Metformin	30 (32.6%)	36 (39.1%)	66 (71.7%)	
Glyburide	1 (1.1%)	1 (1.1%)	2 (2.2%)	
Metformin + Glyburide	12 (13.0%)	12 (13.0%)	24 (26.1%)	

Abbreviations: SD, standard deviation; BMI, body mass index; %A1c, glycated hemoglobin percentage. * Statistically significant, Student´s t test *p*-value < 0.05

A total of 106 ADRs were reported from 42 patients, represented an average of 2.52 ADRs per patient. The cumulative incidence of ADR was 45.65% (42/92). The proportion of ADRs among non-adherent patients was significantly higher than adherent patients (Chi-square test = 4.64; $p = 0.031$). The metformin was the drug most frequently associated with ADRs in non-adherent patients (Chi-square test = 4.94; $p = 0.026$). Gastrointestinal disorders was the System Organ Class (SOC) most affected (n= 51 ADRs, 48.11%).

The causality of the ADRs was mostly "probable" and occurred in a higher percentage in non-adherent patients (62.96%) according to the Naranjo´s causality algorithm. Regarding severity, the "mild" category was the most frequent, and in non-adherent patients it represented 83.33%. (see Table 2)

Table 2 Characteristics of patients and ADR according to adherence

Characteristics	**Non-adherent**	**Adherent**	**Total**	***P-value***
Number of patients n (%) (total of 92 patients enrolled in the study)				
With ADR	20 (60.61)	22 (37.39)	42 (45.65)	0.031*

Without ADR	13 (39.39)	37 (62.71)	50 (54.35)	
Total	33 (100)	41 (100)	92 (100)	
Adverse drug reactions (total of 106 reported ADRs from 42 patients)				
Antidiabetic drug involved n (%)				
Metformin	47 (87.04)	36 (69.23)	83 (78.30)	0.026*
Glyburide	7 (12.96)	16 (30.77)	23 (21.70)	
Total	54 (100)	52 (100)	106 (100)	
System organ class affected n(%)				
CD	1 (1.85)	0	1 (0.94)	1$^{\delta}$
ED	1 (1.85)	0	1 (0.94)	1$^{\delta}$
MND	1 (1.85)	1 (1.92)	2 (1.89)	1$^{\delta}$
PD	1 (1.85)	4 (7.69)	5 (4.72)	0.201$^{\delta}$
SSD	2 (3.70)	4 (7.69)	6 (5.66)	0.433$^{\delta}$
GDAC	4 (7.41)	3 (5.77)	7 (6.60)	1$^{\delta}$
NSD	18 (33.33)	15 (28.85)	33 (31.13)	0.672
GD	26 (48.15)	25 (48.08)	51 (48.11)	0.994
Total	54 (50.94)	52 (49.06)	106 (100)	
Causality assessment n (%)				
Probable	34 (62.96)	25 (48.08)	59 (55.66)	0.123
Possible	20 (37.04)	27 (51.92)	47 (44.34)	
Total	54 (100)	52 (100)	106 (100)	
Severity assessment n (%)				
Mild	45 (83.33)	48 (92.31)	93 (87.74)	0.237 $^{\delta}$
Moderate	9 (16.67)	4 (7.69)	13 (12.26)	
Total	54 (100)	52 (100)	106 (100)	

* Statistically significant, Chi-square test p-value < 0.05; $^{\delta}$ Comparative analysis was performed by Fisher´s exact test

Abbreviations:

- CD = cardiac disorders;
- ED = eye disorders;
- MND = metabolism and nutrition disorders;
- PD = psychiatric disorders;
- SSD = skin and subcutaneous tissue disorders;
- GDAC = general disorders and administration site conditions;
- NSD = nervous system disorders
- GD = gastrointestinal disorders.

4. Discussion

To the best of our knowledge, this is the first prospective study where the presence of ADRs and pharmacotherapeutic adherence are jointly analyzed in patients with antidiabetic therapy in the southern Mexican population. This study found that ADRs associated with the use of oral antidiabetic therapy is more common in non-adherent patients, manifesting mainly through gastrointestinal disorders. The significance of these findings highlights how ADRs negatively affect treatment adherence in this patient population.

Most patients (71.7%) received metformin as pharmacological treatment, aligning with clinical practice guidelines for T2D management, including the Mexican Clinical Practice Guideline (MCPG) [4], and the American Diabetes Association (ADA) [11]. These guidelines recommend metformin as a first-line therapy, with a second-line addition like glyburide if glycemic control is insufficient.

Similar patterns of medication use in this study have been noted by previous research. For example, Kumar et al. [12] reported metformin use in 98.52% of outpatients with T2D in India. Elangwe et al. [13] found 83.4% metformin use among outpatients in a Cameroonian tertiary diabetes care service. Fierro et al. [14] in a retrospective study in a Mexican tertiary hospital, showed metformin as the most prescribed oral antidiabetic over four years, used either in monotherapy (38%) or with other antidiabetic drugs (62%, primarily glyburide).

Pharmacological treatment adherence was another key variable. The study found that 35.87% (n=33) of patients were non-adherent, consistent with studies in Mexico and Latin America that report non-adherence rates between 40% and 70% in T2D patients [15-22].

Lack of adherence to oral antidiabetic treatment represents one of the main barriers to achieving adequate glycemic control and constitutes a significant risk factor for the development of diabetic complications and hospitalization [23,24]. Additionally, the presence of ADRs associated with antidiabetic pharmacotherapy can negatively affect adherence, which highlights the importance of considering both variables together [25].

In our study, 45.65% (n=42) of patients presented at least one ADR, of which 60.61% (n=20) were not adherent to treatment. We observed that the presence of ADRs is more frequent in non-adherent patients, with a statistically significant association (p=0.031). Elangwe et al. [13] found in a study conducted in Cameroon that the proportion of ADRs in patients with low adherence was higher than in adherent patients (p = 0.007). A study conducted in Spain in community pharmacies with patients on drug treatment for DT2, found that the presence of hypoglycemic events (adverse drug reaction) was one of the main factors associated with low adherence to treatment [26]. In contrast, a study conducted by Marcianó et al. in Italy did not find a statistically significant association between the presence of ADRs and the degree of pharmacotherapeutic adherence, suggesting that socioeconomic factors and ethnicity probably play a role in adherence to treatment [27].

In agreement with other reports, gastrointestinal disorders (GD) were the most common [28, 29]. These adverse effects are known to be common during treatment with metformin. However, they are usually mild and disappear when the dose is reduced or the drug is stopped [30]. In the present study, nervous system disorders (NSD) were identified with a frequency of 31.13%, including headaches, tremors, drowsiness and anxiety. These symptoms are characteristic of hypoglycemic episodes and occur more frequently in patients treated with drugs that increase insulin secretion, such as sulfonylureas (e.g. glyburide). In addition, they may affect almost half of diabetic patients and are associated with increased mortality in this group [31]. These findings highlight the importance of providing adequate patient education to identify and report these adverse events, as well as individualizing drug selection to minimize these risks. Causality assessment using the Naranjo´s algorithm indicated that most ADRs were classified as probable (68.81%), while the rest were considered possible. Regarding severity, 87.74% of ADRs were mild, which is consistent with previous reports and with the safety profile of the drugs evaluated [32,33].

A limitation of our study was that, despite the longitudinal design used, no ADRs with definitive causality were identified. This may be attributed to the method used for their assessment (Naranjo algorithm), which requires, to classify an ADR as definitive, re-exposure to the drug or quantification of its serum levels. However, these actions were not possible due to ethical and safety considerations, as well as the lack of infrastructure for measuring serum drug levels. This limitation could be addressed by using other causality assessment algorithms in conjunction with Naranjo's, such as the modified Karch-Lasagna or the WHO algorithm [34,35].

5. Conclusion

This study provides objective evidence on the relationship between poor adherence to oral hypoglycemic treatment and a higher prevalence of ADRs using real-world data. While the identified ADRs were mild and not life-threatening, they could still compromise the achievement of therapeutic goals. Therefore, continuous monitoring and early detection of these reactions are recommended, along with the implementation of strategies to improve therapeutic adherence.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that no competing interests exist.

Statement of ethical approval

The study was approved and authorized by the hospital's Research Committee and by the Research Ethics Committee.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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