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SHORT COMMUNICATION

Photosensitivity with Angiotensin II Receptor Blockers: A Retrospective Study Using Data from VigiBase®

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Abstract

Background Angiotensin II receptor blockers (ARBs) are widely used to treat hypertension and heart failure. Photosensitivity reactions are cutaneous adverse events due to exposure to a drug and either ultraviolet or visible radiation. Among the ARB class, this type of adverse drug reaction is labeled only for losartan.

Objective The aim of this study was to provide a descriptive evaluation of photosensitivity reports with ARBs in the World Health Organization Global Individual Case Safety Report database, VigiBase®.

Methods All reports of photosensitivity reported with ARBs were identified from VigiBase®. All variables contained in the reports were analyzed. Information component (IC) and its lower limit of a 95 % credibility interval (IC_{025}) values were considered as measures of disproportionality for the assessment of photosensitivity cases reported with ARBs. VigiGrade completeness score (*C*) was used as a measure of quality of each report. Well-documented reports ($C > 0.8$) were fully described and analyzed.

Results Up to December 2014, a total of 203 reports on photosensitivity reported with ARBs and submitted by 25 different countries had been recorded in VigiBase®. Among them, 25.1 % involved losartan, 23.1 % involved irbesartan, and 21.7 % involved valsartan. In 126 cases, the ARB was the only suspected drug and in 10 % of them the reaction was serious. IC and IC_{025} values indicated a possible positive correlation between photosensitivity and both irbersartan and losartan. A focus on well-documented reports, after excluding those with a co-prescription of other drugs known to cause photosensitivity, showed that out of 18 cases, six were related to losartan, four to olmesartan, three to irbesartan, two to valsartan and to candesartan, and one to telmisartan. Causality assessment was 'probable' in ten cases and 'possible' in eight cases. Moreover, positive dechallenge was reported in ten cases and positive rechallenge in one case.

Conclusions Photosensitivity reactions have been reported with almost all ARBs in VigiBase® with a positive disproportionality for irbesartan and losartan. Considering that ARBs share the same chemical structure, which may have the same response to sunlight, it is plausible to consider photosensitivity as a possible class effect. Physicians and patients should be aware of potentially serious photosensitivity reactions related to treatment with ARBs.

Key Points

Angiotensin II receptor blockers (ARBs) are identified as drugs suspected of inducing photosensitivity reactions in more than 200 reports extracted from the World Health Organization Global Individual Case Safety Report database, VigiBase®.

Data of well-documented reports, causality assessment, dechallenge, and rechallenge information suggest a possible association between photosensitivity and the use of ARBs.

Physicians and patients should be aware of potentially serious photosensitivity reactions related to treatment with ARBs.

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1 Introduction

In susceptible patients, the interaction between sunlight and medications may lead to photosensitivity reactions, either in the form of a phototoxic reaction or photoallergy. Phototoxicity is defined as an acute light-induced tissue response to a photoreactive chemical, whereas photoallergy is an immunologically mediated reaction to a chemical initiated by the formation of photoproducts following a photochemical reaction [1, 2].The prevalence of drug-induced photosensitivity is not known exactly and probably underdiagnosed, but phototoxicity has a higher incidence compared to photoallergy [3]. This reaction may occur in everyday life, e.g., during outdoor work, sports, or in travel [4, 5]. Systemic drug photosensitivity occurs mostly because of a phototoxic mechanism, whereas photoallergy more often occurs as a result of topical agents; however, topical drugs may also cause photosensitivity through a phototoxic mechanism. There is a long list of both topical and systemic photosensitizing drugs [6]; however, data are mainly collected from case reports and case series. Among the drug classes currently eliciting a high number of adverse photosensitivity reactions there are antibacterial and nonsteroidal anti-inflammatory drugs, while single photosensitizing medications include amiodarone, chlorpromazine, thioridazine, and voriconazole. Among antihypertensive medications, diuretics, such as hydrochlorothiazide, are well known to cause photosensitivity and some ACE inhibitors acting on the renin-angiotensin-aldosterone system have also been reported to cause phototoxicity with positive photo patch testing results and rechallenge evidence for ramipril and quinapril [1].

Prevention of photosensitivity involves adequate protection from the sun with clothing and sunscreens. Sun avoidance is recommended in patients exposed to known photosensitizers but the list of new drugs reported to have photosensitizing properties is continuously growing. Therefore, drug-induced photosensitivity is an ongoing problem and any new findings should be taken into account.

Currently, eight angiotensin II receptor blockers (ARBs) mainly indicated to treat essential hypertension are on the market worldwide, azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. Fimasartan is only approved in South Korea.

In the Summary of Product Characteristics of USA and in the majority of European countries, photosensitivity is not labeled for ARBs [7–9], with the exception of losartan, and it is not reported in Micromedex® [10]. The mechanism by which losartan causes photosensitivity is still unknown. Moreover, Frye et al. described a case of angioedema and photosensitive rash in a 71-year-old woman after 3 months of therapy with valsartan [11].

The present study aims to perform a descriptive evaluation of the possible causal relationship between ARBs and the onset of photosensitivity after patient sun exposition, by using the spontaneous reporting system as an effective tool for early detection of the safety signal.

2 Methods

This retrospective descriptive study is based on selected individual case safety reports (ICSRs) of photosensitivity reactions associated with ARBs collected from the World Health Organization (WHO) Global ICSR database, VigiBase® [12]. VigiBase® was established in 1968 and is maintained by the Uppsala Monitoring Centre (UMC). To date, VigiBase® contains more than 10 million ICSRs. National centers participating in the WHO Program for International Drug Monitoring report to the UMC suspected ADRs due to drug use. Currently, 120 member countries submit ICSRs to VigiBase®.

Serious adverse reactions are defined as any adverse medical occurrence that results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening. Cancers and congenital anomalies or birth defects and medical events, which had not responded to acute treatment, should also be considered serious [13].

2.1 Recording of Individual Photosensitivity Case Safety Records

Reports up to December 2014 of photosensitivity reactions related to ARBs were collected from the WHO Global ICSR database, VigiBase®, and consequently assessed. Suspected adverse drug reactions (ADRs) were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA® 17.1).

Cases of photosensitivity have been defined as reports associated with at least one of the following MedDRA® terms: 'photosensitivity and photodermatosis conditions' (high-level term) or 'solar urticaria' (preferred term). To assess the causal relationship between ARBs and photosensitivity reactions, all available variables contained in the reports were analyzed: demographic characteristics, ADR description, times of onset and ending of reaction, latency period, seriousness and outcome, concomitant drugs, and information about drug dechallenge and rechallenge. Narratives were also consulted when available.

The information component (IC) was considered as a measure of disproportionality for a specific drug–ADR

combination. A positive IC value indicates that a particular drug–ADR combination has been reported more often than expected, based on all the reports in the database. The IC was obtained for the combination of MedDRA® preferred terms under investigation and each ARB excluding eprosartan (only one ICSR). The IC_{025} value is the lower limit of a 95 % credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability. For each IC, we considered the IC_{025} as a measure of the strength of the value. The IC does not imply causality of a potential adverse reaction induced by a drug. The IC shows the quantitative dependency between the ADR and the drug, based on the reporting to the WHO Global ICSR database. If the IC value increases over time and the IC_{025} value is positive, the likelihood of a positive quantitative association between the drug and the adverse reaction is high, although clinical assessment remains essential [14].

2.2 Extraction of Well-documented Individual Photosensitivity Case Safety Records

To identify well-documented ICSRs, we used the vigiGrade *C*, a tool recently developed by the UMC, which measures the amount of information available in structured format on individual case reports. The dimensions accounted for vigiGrade are: time to onset, indication, ADR outcome, patient sex, age, drug dose, country, primary reporter, report type, and comments [15]. The vigiGrade *C* of ADR reports in VigiBase® ranges from 0.07 to 1; reports having $C > 0.8$ are defined as well documented. This threshold requires all important ICSR dimensions (patient sex and age, time to onset, outcome, indication) to be provided and allows at most two of the supportive dimensions to be missing (dose, country, primary reporter, report type, and comments).

ARB-associated photosensitivity ICSRs with $C > 0.8$ have been identified and furtherly screened for other suspected or concomitant drugs for which photosensitivity was labeled in the Summary of Product Characteristics or listed in Micromedex®. For each ICSR, the causality assessment was calculated by authors using the Naranjo algorithm [16].

3 Results

Up to 31 December 2014, there were 203 reports of photosensitivity reactions reported with ARBs in the WHO Global ICSR database, VigiBase®. One hundred and twenty patients were female (59 %), 76 were male (37 %), and in seven cases sex was not reported. The median age was 56 ± 12.3 years. Seriousness was reported only in 99 cases, of which 30 cases reported a serious reaction. In 126 cases, ARB was the only suspected drug and in 133 cases the reporter was a physician. Fifty-one of 203 cases involved losartan (25.1 %), 47 involved irbesartan (23.1 %), 44 involved valsartan (21.7 %), and 35 candesartan (17.2 %). Fewer reports involved telmisartan (15) and olmesartan (11) and only one involved prosartan. No reports with fimasartan were found in the database. The percentage of photosensitivity reports for each ARB in relation to the total number of reports in VigiBase® was higher for irbesartan (0.58 %) followed by losartan (0.41 %), candesartan (0.39 %), valsartan (0.30 %), olmesartan (0.26 %), and telmisartan (0.21 %). Photosensitivity reaction appeared to be the most common term used for coding this type of reaction; in a few cases, photodermatosis, solar dermatitis, and solar urticaria were used. ICSRs were submitted from 25 different countries: the most representative countries were France (51 reports), USA (26 reports), UK (23 reports), and Australia (22 reports).

The IC, considered as a measure of disproportionality for photosensitivity, was positive for both irbersartan and losartan (IC 1.07; IC_{025} 0.62 and IC 0.60; IC_{025} 0.18, respectively), meaning that these combinations stand out against the background of the database. Both IC and IC_{025} values were negative for photosensitivity associated with olmesartan and telmisartan (Table 1).

Among the 203 reports of photosensitivity associated with ARBs, 28 were identified as well documented on the basis of a vigiGrade $C > 0.8$. (13.8 % of the total). Within this group of well-documented reports, we excluded reports listing other drugs known to cause photosensitivity (both suspected and concomitant) and we fully described the remaining 18 ICSRs. Of these, six were related to losartan, four to olmesartan, three to irbesartan, two to valsartan and to candesartan, and one to telmisartan. They came from ten countries of different climatic zones, in particular Spain (four reports), the UK (three reports), Australia, the Netherlands, and France (two reports each). The mean age of patients was 63.15 ± 13.2 years with a prevalence of women (67 %). In 77 % of cases, patients fully recovered or were recovering, while in one patient a recovery with sequelae was reported. Time to onset of photosensitivity in relation to the start of drug therapy showed a great variability (from 1 day to 32 months) with an average of 100 days, but the time of sun exposure was not reported. In four cases, photosensitivity was defined as serious and in two of them hospitalization was referred. The reports were submitted by physicians in 61 % of cases. Causality assessment, calculated by the authors, was 'probable' in ten cases and 'possible' in the remaining eight. Positive dechallenge was reported in ten patients and positive rechallenge in one (detailed data are displayed in Table 2).

Table 1 Individual case safety reports of photosensitivity associated with ARB use in VigiBase®

ARB (reporting years)	Total no. of reports in VigiBase	ADR PT[a]	No. of reports	IC[b]	IC_{025}[b]	No. of countries	Positive dechallenge	Positive rechallenge
Candesartan (1998–2014)	9056	Photosensitivity reaction	32	0.38	−0.16	14	8	2
		Solar urticaria	2	2.13	−0.46	2	1	0
		Photodermatosis	1	1.19	−2.61	1	0	0
Irbesartan (1999–2014)	8036	Photosensitivity reaction	46	1.07	0.62	12	10	2
		Solar dermatitis	1	1.36	−2.44	1	0	0
Losartan (1995–2014)	12,149	Photosensitivity reaction	50	0.60	0.18	15	12	0
		Photodermatosis	1	1.07	−2.73	1	0	0
Olmesartan (2005–2014)	4167	Photosensitivity reaction	9	−0.31	−1.40	6	4	0
		Solar dermatitis	1	1.46	−2.33	1	1	0
		Photodermatosis	1	1.39	−2.41	1	1	0
Telmisartan (2000–2014)	7016	Photosensitivity reaction	15	−0.33	−1.15	6	6	1
Valsartan (1997–2014)	14,656	Photosensitivity reaction	44	0.15	−0.30	10	7	0

ARB angiotensin II receptor blocker

[a] *ADR PT* preferred terms according to the *Medical Dictionary for Regulatory Activities* dictionary

[b] *IC* information component and IC_{025} lower limit of a 95 % credibility interval for the IC, extracted up to 3rd February 2015

4 Discussion

Drug-induced photosensitivity is an ongoing problem and may be prevented only if the drug is known to be a photosensitizing agent [6, 17]. Our study shows that VigiBase® contains 203 voluntary reports of photosensitivity with most ARBs submitted by 25 countries with a positive dechallenge in about 25 % of the cases. In more than 60 % of cases, ARB was the only suspected drug and the reporter was a physician. The authors expected to register a positive IC value for losartan, the only ARB for which photosensitivity is labeled, but the measure of disproportion was positive also for the irbesartan–photosensitivity combination, demonstrating a quantitative dependency between the ADR and the drug. With more than 100 countries participating on a regular basis, VigiBase® is a unique and special resource in signal detection; however, there is high heterogeneity that affects the quality of reports.

The UMC has recently analyzed ICSRs in VigiBase® from 2007 to 2012, showing that only 13 % of them could be considered well documented, achieving a $C > 0.8$. [15]. In line with such analysis, the percentage of well-documented ARB-associated photosensitivity reports was 13.8 %. Well-documented reports, in which no other concomitant photosensitizing drug was reported, are referred in association with every ARB from numerous countries belonging to different climatic zones. The data contained in these selected ICSRs allowed the calculation of a probable causality assessment between ARBs and photosensitivity in 55 % of cases and a possible causal association in the remaining 45 %.

An important limitation of this study is related to the fact that diagnosis or even suspicion of drug-induced photosensitivity is not obvious and the reaction is frequently underdiagnosed [17]. Moreover, ADR spontaneous reporting databases are known to be globally affected by underreporting, with an estimate of global reporting levels representing no more than 5–10 % of the real incidence of ADRs [18]. Underreporting is often the result of obstacles related to organizing the hospital pharmacovigilance system, the workload of usual clinical activities, the lack of time for filling in records, the lack of knowledge of the pharmacovigilance system, the uncertainty of the ADR diagnosis, and the potential conflicts derived from reporting ADRs [19].

In particular, methodological limits have to be considered for the assessment of photosensitivity signals. The time to onset of an adverse reaction is usually important in causality assessment, but considering that the sunlight is the necessary trigger for the onset of photosensitivity, it might not be helpful in the assessment of the causal association of ARBs with photosensitivity. Other relevant limits are represented by the lack of important information in the ICRSs, such as patient skin type or solar radiation dose and the effective time of exposure. The possibility of accidental photodermathoses as a confounder may also have affected the results.

Our findings suggest that photosensitivity could occur in patients treated with ARBs after sun exposure. In our opinion, the awareness of this possible risk may allow patients and physicians to consider preventive measures. Patients could benefit from the use of broad-spectrum sunscreens, protective clothing, or the avoidance of exposure to sunlight and, where possible, physicians should consider changing therapy.

Table 2 Characteristics of 'well-documented' ICSRs of photosensitivity in patients taking ARBs without co-prescription of other photosensitizing drugs up to 31 December 2014

Sex/age (years)	C[a]	Suspected drug	Source	Time to onset (days)	Outcome	Dechallenge/rechallenge	Causality[b]
F/57	0.95	Losartan	Physician	180	Recovered	Positive dechallenge/negative rechallenge	Possible
F/57	0.95	Losartan	Physician	7	Not recovered	NS	Possible
F/75	0.95	Losartan	Physician	4	Recovered	NS	Probable
F/81	0.95	Losartan	Physician	212	Recovering	Positive dechallenge	Probable
F/67	0.90	Losartan	Physician	30	Recovered	Positive dechallenge	Probable
M/57	0.81	Losartan	Pharmacist	1	Not recovered	NS	Possible
F/78	1.00	Irbesartan	Physician	8	Recovered with sequelae	NS	Probable
M/60	0.81	Irbesartan	Physician	34	Recovering	Positive dechallenge	Probable
M/55	0.95	Irbesartan	Other	120	Recovered	NS	Possible
F/56	1.00	Olmesartan	Physician	15	Recovered	NS	Possible
M/63	1.00	Olmesartan	Pharmacist	39	Recovered	Positive dechallenge	Probable
M/60	1.00	Olmesartan	Consumer/non-health professional	1	Not recovered	Positive rechallenge	Probable
F/67	0.81	Olmesartan	Physician	32 months	Recovered	Positive dechallenge	Probable
F/38	1.00	Candesartan	Consumer/non-health professional	23	Recovering	Positive dechallenge	Possible
M/49	0.95	Candesartan	Physician	122	Recovered	Positive dechallenge	Probable
F/81	1.00	Valsartan	Physician	14	Recovered	Positive dechallenge	Probable
F/71	1.00	Valsartan	Pharmacist	8	Not recovered	NS	Possible
F/68	0.90	Telmisartan	Pharmacist	1	Recovered	NS	Possible

ARB angiotensin II receptor blocker, *F* female, *ICSRs* individual case safety reports, *M* male, *NS* not specified

[a] vigiGrade completeness score [15]

[b] Causality assessment calculated by authors according to the Naranjo algorithm [16]

5 Conclusions

The list of drugs causing photosensitivity is very large and always increasing. Our findings suggest a possible association between photosensitivity and the use of ARBs. Because we gathered photosensitivity reports from VigiBase® for each ARB and considering that ARBs share the same chemical tetrazolo-biphenyl structure as losartan, which may have the same response to sunlight, it is plausible to consider photosensitivity as a possible class effect.

Although further studies are needed to confirm our hypothesis, to recognize and avoid these potentially serious cutaneous reactions, physicians and patients should be aware of this possible risk.

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Compliance with Ethical Standards

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Conflicts of Interest Ermelinda Viola, Anna Coggiola Pittoni, Agnes Drahos, Ugo Moretti, and Anita Conforti have no conflicts of interest that are directly relevant to the content of this study.

References

1. Drucker AM, Rosen CF. Drug-induced photosensitivity: culprit drugs, management and prevention. Drug Saf. 2011;34(10):821–37.
2. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. Drug Saf. 2002;25(5):345–72.
3. Verdel BM, Souverein PC, Meyboom RH, Kardaun SH, Leufkens HG, Egberts AC. Risk of drug-induced photosensitivity: focus on spectroscopic and molecular characteristics. Pharmacoepidemiol Drug Saf. 2009;18(7):602–9. doi:10.1002/pds.1760.
4. Ciocca M. Medication and supplement use by athletes. Clin Sports Med. 2005;24(3):719–38.
5. Diaz JH, Nesbitt LT Jr. Sun exposure behavior and protection: recommendations for travelers. J Travel Med. 2013;20(2):108–18.
6. Dawe RS, Ibbotson SH. Drug-induced photosensitivity. Dermatol Clin. 2014;32(3):363–8.
7. National Library of Medicine. DailyMed. Available at: http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed 2015 Mar 04.

8. Agenzia Italiana del farmaco. Banca dati farmaci. Available from http://farmaci.agenziafarmaco.gov.it/bancadatifarmaci. Accessed 2015 Mar 04.
9. Datapharm Communications Limited. Electronic medicines compendium. Available at: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm. Accessed 2015 March 04.
10. The evidence-based resources of Micromedex® Solutions. Drug: detailed evidence-based information (DRUGDEX®). Available from http://www.micromedexsolutions.com. Accessed 2014 July 10.
11. Frye CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsartan. Pharmacotherapy. 1998;18(4):866–8.
12. World Health Organization. VigiBase® the WHO Global ICSR database system. Available from http://who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326.
13. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356(9237):1255–59.
14. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315–21.
15. Bergvall T, Norén GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Saf. 2014;37(1):65–77.
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45.
17. Goncalo M. Phototoxic and photoallergic reactions. In: Johansen JD, et al., editors. Contact dermatitis. Berlin Heidelberg: Springer Verlag; 2010.
18. Hazell L, Shakir SA. Underreporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96.
19. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32(1):19–31.