Drug effects on melanoma

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Chapter 7

Melanoma Incidence and Exposure to Angiotensin-converting enzyme Inhibitors and Angiotensin Receptor Blockers

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Abstract

Background: A reduced incidence of nonmelanoma skin cancer among users of Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin Receptor blockers (ARb) has been reported. A similar effect is suggested for cutaneous melanoma. We aimed to investigate the possible association between use of ACEi and ARb and the risk of cutaneous melanoma .

Patients and Methods: A general population-based case control study with the PHARMO database, containing drug-dispensing records from community pharmacies and the national pathology database (PALGA) was conducted. Cases were patients with a primary cutaneous melanoma between January 1st 1991 and December 14th 2004, aged ≥ 18 years and having ≥ 3 years of follow-up prior to diagnosis.

Results: Finally, 1272 cases and 6520 matched controls were included. Multivariable conditional logistic regression showed no statistically significant associations between the incidence of melanoma and the use of ACEi (adjusted odds ratio (OR) = 1.0, 95% CI = 0.8-1.3) or ARb (adjusted OR = 1.0, 95% CI = 0.7-1.5).

Conclusion: In this study, the use of ACEi or ARb does not seem to protect against the development of cutaneous melanoma. However, we cannot exclude an association between ACEi and ARb exposure and an increased or decreased incidence of cutaneous melanoma.

Introduction

Chemopreventive effects in cancer have been suggested for angiotensin-converting enzyme (ACEi) inhibitors and angiotensin receptor (ARb) blockers in both *in vitro* studies, animal studies and epidemiologic studies. [1-6] *In vitro* and *in vivo* effects have been demonstrated on cell proliferation, gene expression, migration and invasion and angiogenesis. [1] These effects may be mediated through angiotensin II or bradykinin. [1] However, other mechanisms, such as inhibition of metalloproteases [4], reduction of the activity of plasminogen activator inhibitor-I [7], generation of angiostatin from plasmin [8] or activity as a free-radical scavenger [9] if a free sulhydryl donor is present in the molecule, e.g., captopril and zofenopril, may also be involved. Depending on which mechanisms are involved, chemopreventive effects may be considered to be an overall class effect for both ACEi and ARb, may be present for only ACEi or may be restricted to exposure to ACEi with a certain chemical structure.

In human head and neck squamous skin cancer cells, Yasumatsu and Nakashima observed a significant inhibitory effect on tumor growth and blood vessel formation mediated by perindopril. [5] Specifically for cutaneous melanoma, an *in vitro* study showed that captopril has antitumor activity in a human melanoma xenograft model. [10]

For melanoma, chemoprevention is of special interest because of rapidly increasing incidence (http://www.cancer.org/, Cancer Facts and Figures 2008, accessed February 3rd 2009) and the lack of survival prolonging therapies for advanced disease. [11] Recently, two epidemiological studies among users of ACEi and ARb reported on reduced risks of nonmelanoma skin cancer. [6,12]

With respect to the expected safety profile, ACEi and ARb would be good candidates because they are widely used in clinical practice with few side effects. However, to our knowledge, no observational studies have been performed that specifically investigate the chemoprophylactic properties of ACEi and ARb in melanoma. Therefore, we investigate the potential association between the risk of cutaneous melanoma and exposure to (different chemical drug classes of) angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Patients and methods

Study design

We conducted a general population-based case control study exploring the use of ACEi and ARb among individuals with and without cutaneous melanoma. The protocol

of this study was approved by the scientific and privacy committees of both PALGA and PHARMO, and was granted exempt status by the ethics board of the Leiden University Medical Centre. An outline of the methods is presented here. Additional details are presented in earlier work. [13]

Data were extracted from the PHARMO (PHARmaco MOrbidity) linkage network and the PALGA database. PHARMO contains virtually complete drug-dispensing records of over 2 million Dutch residents, included regardless of the type of health insurance or other relevant factors and representing >12% of the Dutch population (http://www.pharmo.nl, Databases, accessed October 7th 2009). These computerized drug-dispensing histories contain all dispensed prescriptions and include type, quantity, dosage form, strength, dispensing date and prescribed daily dose of the dispensed drug.

PALGA is the Nationwide Network and Registry of Histo- and Cytopathology and contains pathology abstracts with diagnostic terms in scope with SNOMED classification of all Dutch patients (100% registration since 1990) and is the source of the Netherlands Cancer Registry. PHARMO and PALGA are linked using a variation of a reliable probabilistic algorithm. [14,15]

Two investigators read all pathology reports to validate the melanoma diagnoses. Interobserver variation was assessed on 300 randomly selected cases.

Cases were included if they had a primary diagnosis of cutaneous melanoma between January 1st 1991 and December 14th 2004 in PALGA, were aged 18 years or older at diagnosis and had at least 3 years of complete follow-up in PHARMO prior to diagnosis. For every case, an average of five controls, matched for age (± 2 years), gender, and geographical region, was included. To calculate follow-up, controls were assigned the index date of the matched case. Potential controls were excluded if, in PHARMO, a date of entry was unknown, they were younger than 18 years at the index date, follow-up in the 3 years before index date was incomplete or if they were diagnosed in PHARMO with previous melanoma according to the International Classification of Disease. If more controls were elligible, the excess number of controls was randomly deleted.

Drug exposure

For cases and controls, dispenses of all commercially available ACEi and ARb (Anatomical Therapeutic Classification (ATC) codes: C09AAxx and C09CAxx), restricted to the 3-year observation period before the index date, were included. To avoid misclassifying cases and controls as ACEi or ARb users, drug exposure was defined as at least 6 months of cumulative prescription duration in the 3 years before melanoma

(e.g., after one or two first dispenses patients may discontinue for several reasons, effects on melanoma incidence of such short periods of use are considered to be unlikely).

ACEi were further classified in three drug classes according to their chemical structure (Table 1).

The level of exposure to ACEi and ARb was expressed in defined daily doses (DDD) according to WHO definitions (http://www.whocc.no/atcddd/indexdatabase/, last accessed February 6th 2009). Drug exposure was further detailed with three additional drug exposure variables, all with the 6-month threshold. In explanation, the cumulative dispensed dose, the cumulative prescribed duration and the average day dose within the 3-year period were calculated. The average day dose was defined as the cumulative dose divided by the cumulative duration. We categorized these drug exposure variables across tertiles or the median depending on the number of users.

Table 1 Chemical drug class and ATC codes for commercially available ACE inhibitors

ATC code	Generic drug name	Chemical drug class
C09AA01	Captopril	Sulfhydryl
C09AA02	Enalapril	Carboxyl
C09AA03	Lisinipril	Carboxyl
C09AA04	Perindopril	Carboxyl
C09AA05	Ramipril	Carboxyl
C09AA06	Quinapril	Carboxyl
C09AA07	Benazepril	Carboxyl
C09AA08	Cilazapril	Carboxyl
C09AA09	Fosinorpil	Phosphoryl
C09AA10	Trandalopril	Carboxyl
C09AA11	Spirapril	Carboxyl
C09AA13	Moexipril	Carboxyl
C09AA15	Zofenopril	Sulfhydryl

ATC code= Anatomical Therapeutic Classification code.

Potential confounders

Ever drug use of drugs possibly related to progression or development of melanoma, statins, estrogens and non-steroidal anti-inflammatory drugs were considered as potential confounders. [16] Use of fibrates and lipid-lowering drugs other than fibrates or statins was recorded, but the number of cases and controls using these drugs were too small to be used in further analysis. To test as an additional potential confounder, the total number of unique (singular) codes of the International Classification of Disease 9th revision, as an estimate of health care consumption which may affect the likelihood of melanoma diagnosis, was calculated for each participant in the 3 years before diagnosis.

Statistical analysis

A multivariable conditional logistic regression model was used to calculate adjusted OR and 95% confidence interval (CI) for the association between incident cutaneous melanoma and the use of ACEi and ARb. Potential confounders (the total number of unique medical diagnoses, ever drug use of in the 3-year period of respectively statins, estrogens, and non-steroidal anti-inflammatory drugs) were included in the multivariable model if they influenced the regression coefficient by 10% or more. [17] In sensitivity analyses, stratification across the chemical drug class was performed because some of the reported mechanisms of actions would predict chemopreventive effects only for ACEi with a certain chemical structure (see introduction). Additionally, separate analyses were performed for men and women. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

Study population

In the baseline study, 1,318 melanoma cases and 6,786 matched controls were included.13 Of these, 46 cases and 266 controls were excluded because they used an ACEi or ARb for less than 6 months. The mean age of the cases and controls was respectively 54.9 years [standard deviation (SD) 15.9] and 55.5 years [SD 15.4] (Table 2). Accordance between two investigators on the validation of melanoma diagnosis was high (Kappa value > 0.85) in a random sample of 300 cases, suggesting small interobserver variation.

Exposure to ACE inhibitors and AR blockers

ACEi were used by 85 cases (7%) and 433 controls (7%). Among the ACEi users, 401 (92%) used a carboxyl derivative, 106 (24%) used a sulfhydryl derivative and 24 (6%)

Table 2 Characteristics of the study population

	Cases (n = 1272)		Controls (n = 6520)	
	n	**%**	**n**	**%**
Gender				
male	519	(41 %)	2598	(40 %)
female	753	(59 %)	3922	(60 %)
Drug use				
ACE inhibitor users [a]	85	(7 %)	433	(7 %)
Carboxyl [a,b]	65	(5 %)	332	(5 %)
Sulfhydryl [a,b]	19	(2 %)	87	(1 %)
Phosphoryl [a,b]	2	(0.2 %)	22	(0.3 %)
AR blocker [a]	30	(2 %)	148	(2 %)
estrogen users [c,d]	259	(34 %)	1090	(28 %)
statin users [c]	104	(8 %)	511	(8 %)
NSAID users [c]	591	(47 %)	2740	(42 %)
Total unique diagnoses				
mean number		0.7		0.6
Age at diagnosis [e]				
18-34 yr	134	(11 %)	579	(9 %)
35-44 yr	223	(18 %)	1125	(17 %)
45-54 yr	274	(22 %)	1445	(22 %)
55-64 yr	259	(20 %)	1384	(21 %)
65-74 yr	223	(18 %)	1159	(18 %)
75 yr and older	159	(13 %)	828	(13 %)

[a] At least 6 months of drug use.
[b] See Table 1 for chemical drug class classification of ACE inhibitors.
[c] Ever drug use.
[d] Females only, 753 cases and 3922 controls.
[e] Cases: mean ± standard deviation: 54.9 years ± 15.9 years and range: 18-94 years;
Controls: mean ± standard deviation: 55.5 years ± 15.4 years and range: 18-95 years.

ACE = Angiotensin-Concerting Enzyme, AR = Angiotensin Receptor,
NSAID = Non-steroidal Anti Inflammatory Drug.

used a phosphoryl derivative. ARb were used by 30 cases (2.5%) and 148 controls (2.4%). Cases and controls using ACEi or ARb was prescribed a median average day dose of 1.0 DDD per day (interquartile range: 0.7-2.0 DDD) and 1.0 DDD per day (interquartile range: 1.0-1.8 DDD), respectively. The use of ACEi was not significantly

associated with the incidence of cutaneous melanoma (adjusted OR = 1.0; 95% CI = 0.8-1.3). Increasing cumulative prescription duration, cumulative dose or average day dose also did not show a statistically significant effect of ACEi on cutaneous melanoma incidence (Table 3). After adjustment for age at melanoma diagnosis and the number of medical diagnoses, the use of ACEi was not associated with a decreased Breslow thickness (estimated percentage change in Breslow depth: 2.1%, 95% CI: -17.4% to 26.2%). We previously described the calculation method used. [13]

For ARb no significant associations were demonstrated if users (>0.5 year) are compared to non-users (adjusted OR = 1.1; 95% CI = 0.7-1.5) and if among them the cumulative prescription duration, cumulative dose or average day dose was compared (Table 3). The use of ARb was also not associated with a decreased Breslow thickness after adjustment for the number of medical diagnoses and age at melanoma diagnosis (2.4%, 95% CI = -25.3% to 40.6%).

Sensitivity analysis

Stratification across the three chemical drug classes was performed in a sensitivity analysis. For carboxyl and sulfhydryl ACEi, the association was similar to the results for the overall effect of ACEi (adjusted OR = 1.0, 95% CI = 0.8-1.3 and adjusted OR = 1.1, 95% CI =: 0.7-1.7, respectively). Very few cases and controls used phosphoryl ACEi, resulting in a large confidence interval (adjusted OR = 0.6, 95% CI = 0.1-2.4). Additionally, separate analyses for men and women, showed similar results (data not shown).

Discussion

In this study the use of ACEi or ARb does not seem to protect against the development of cutaneous melanoma. However, our study cannot exclude an association between ACEi and ARb exposure and either a (moderately) increased or decreased incidence of cutaneous melanoma. It is, for instance, possible that exposures with a longer duration or to higher doses of ACEi or ARb are needed for an association to be detected.

A decreased Breslow thickness among the cases using ACEi or ARb, as compared to the melanoma patients who did not use ACEi nor ARb, could be considered a clue for this possibility. However, the use of ACEi or ARb was not associated with decreased Breslow depth.

The major strengths of this study were the large population-based sample of pathology confirmed melanoma cases and the prospectively collected and detailed information about drug dispenses. A limitation of the study is the relatively small

Table 3 Prior Use of ACE Inhibitors or Angiotensin II Receptor Antagonists in the Study Population

	Cases		Controls		OR [a]	95% CI
USE OF ACE INHIBITORS [b]						
Users versus non-users	n=1272		n=6520			
	n	**%**	**n**	**%**		
non-exposed	1187	93.3 %	6087	93.4 %	1.0	referent
exposure >0.5 yr	85	6.7 %	433	6.6 %	1.0	0.8 – 1.3
Cumulative prescription duration [c]						
non-exposed	1187	93.3 %	6087	93.4 %	1.0	referent
non-exposed	32	2.5 %	151	2.3 %	1.1	0.7 – 1.5
1-750 days	19	1.5 %	100	1.5 %	1.0	0.6 – 1.5
751-1000 days	34	2.7 %	182	2.8 %	1.0	0.7 – 1.4
Cumulative dose						
0 DDD	1187	93.3 %	6087	93.4 %	1.0	referent
1-600 DDD	26	2.0 %	153	2.3 %	0.9	0.6 – 1.3
601-1200 DDD	33	2.6 %	130	2.0 %	1.2	0.9 – 1.8
> 1200 DDD	26	2.0 %	150	2.3 %	0.9	0.6 – 1.3
Average day dose						
0 DDD/day	1187	93.3 %	6087	93.4 %	1.0	referent
0.01-1.00 DDD/day	45	3.5 %	225	3.5 %	1.0	0.7 – 1.4
1.01-1.50 DDD/day	10	0.8 %	62	1.0 %	0.9	0.5 – 1.6
> 1.5 DDD/day	30	2.4 %	146	2.2 %	1.0	0.7 – 1.5
USE OF AR BLOCKERS [d]						
Users versus non-users	n=1217		n=6235			
non-exposed	1187	97.5 %	6087	97.6 %	1.0	referent
exposure >0.5 yr	30	2.5 %	148	2.4 %	1.0	0.7 – 1.5
Cumulative prescription duration [c]						
non-exposed	1187	97.5 %	6087	97.6 %	1.0	referent
1-750 days	20	1.6 %	70	1.1 %	1.4	0.9 – 2.1
>750 days	10	0.8 %	78	1.3 %	0.7	0.4 – 1.3
Cumulative dose						
0 DDD	1187	97.5 %	6087	97.6 %	1.0	referent
1-1000 DDD	22	1.8 %	82	1.3 %	1.3	0.8 – 2.0
> 1000 DDD	8	0.7 %	66	1.1 %	0.7	0.3 – 1.4
Average day dose						
0 DDD/day	1187	97.5 %	6087	97.6 %	1.0	referent
0.01-1.00 DDD/day	16	1.3 %	89	1.4 %	0.9	0.6 – 1.5
> 1.0 DDD/day	14	1.2 %	59	0.9 %	1.2	0.7 – 2.0

[a] Adjusted for the total number of unique medical diagnoses and the use of statins.
[b] All commercially available ACE inhibitors in The Netherlands between 1991 and 2004.
[c] Time interval between first prescription and estimated last day of use based on last dispense and amount dispensed in the three years before diagnosis of cutaneous melanoma.
[d] All commercially available AR blockers in The Netherlands between 1991 and 2004.
OR = Odds Ratio, CI = Confidence Interval, ACE = Angiotensin-Concerting Enzyme, AR = Angiotensin Receptor.

number of ACEi and ARb users leading to limited statistical precision, especially for the stratified analyses. Another limitation is the relatively short follow-up (3 years). We decided to use only cases and controls with complete follow-up to guarantee that cases and controls were active members of the PHARMO network and thus all prescription drugs dispensed would be registered in PHARMO. Due to sample size limitations, we were not able to study the effects of drug use longer than 3 years before cutaneous melanoma. However, the length of follow-up in our study was comparable with the median follow-up in a previous study in which exposure to ACEi and ARb was significantly associated with reduced risks of basal cell carcinoma and squamous cell carcinoma. [12]

Residual confounding may have affected our findings. ACEi and ARb users are likely to have more health care contacts and therefore might be more likely to be diagnosed with melanoma. We included the number of unique medical diagnoses (ICD codes) in our study to adjust for this. Nevertheless, not all health consumption may be reflected in these diagnoses and ascertainment bias cannot be excluded.

Common risk factors for melanomas, such as family history of melanoma, skin type, sun exposure history and socioeconomic status, are not available in PHARMO and PALGA. Therefore, we could not adjust for these factors. Skin type and family history of melanoma are, in our opinion, unlikely to affect the likelihood of prescription of ACEi and ARb. Thus, confounding by indication by these seems unlikely. Sun exposure, however, may be indirectly related to ACEi and ARb exposure because it may be associated with increased physical activity and a reduced chance of hypertension. Likewise, high social economic status is associated with increased sun exposure and may also be associated with a reduced chance of hypertension. Both these potential biases would in an underestimation of any effect of ACEi and ARb and would thus produce bias toward the null.

An additional source of residual confounding may be exposure to NSAIDs obtained as over-the-counter drugs that will not always be registered in PHARMO. However, such misclassification is likely to be equal among cases and controls; hence, bias is likely to be minimal.

Despite the limitations mentioned, we believe the results of our study with adjusted ORs near to 1.0 emphasize the possibility that ACE inhibitors and AR blockers at current dosage may not affect melanoma development.

Conclusion

In this study, the use of ACEi or ARb does not seem to protect against the development of cutaneous melanoma. However, we cannot exclude an association between ACEi and ARb exposure and an increased or decreased incidence of cutaneous melanoma.

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