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Influence of smoking and smoking cessation on levels of urinary 11-dehydro thromboxane B_2

Angela van der Plas*, Sandrine Pouly, Guillaume de La Bourdonnaye, Wee Teck Ng, Gizelle Baker, Frank Lüdicke

Product Assessment and Scientific Substantiation, Philip Morris International Research & Development, Philip Morris Products S.A., Quai Jeanrenaud 5, 2000 Neuchatel, Switzerland

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ABSTRACT

Background: Thromboxane is a key clinical risk endpoint of smoking-induced inflammation which has been associated in the pathogenesis of cardiovascular disease. The goal of this review is to quantify the effect of smoking and smoking cessation on one of its urinary metabolites, 11-dehydrothromboxane$_{B2}$.

Methods: PubMed and SCOPUS were searched to identify publications which report urinary 11-dehydrothromboxane$_{B2}$ levels in smokers and non-smokers, as well as articles reporting the effect of smoking cessation on urinary 11-dehydrothromboxane$_{B2}$ excretion.

Results: We found ten studies assessing urinary 11-dehydrothroboxane$_{B2}$ levels in smokers and non-smokers. Four papers reported the amount of urinary 11-dehydrothromboxane$_{B2}$ excreted in 24 h while six reported the amount excreted adjusted for creatinine. The meta-analyses comparing the excretion of urinary 11-dehydro-thromboxane in current smokers to non-smokers report increased levels in current smokers (mean difference = 0.31 µg/24-h [95%CI: 0.27–0.34] and 166.45 pg/mg creatinine [95%CI: 120.51–212.40]). There were not enough publications to perform meta-analyses on the effects of smoking cessation on urinary 11-dehydrothromboxane$_{B2}$ excretion.

Conclusions: Urinary 11-dehydrothromboxane$_{B2}$ levels are increased in cigarette smokers, however, more data are needed to elucidate the effects of smoking cessation on urinary 11-dehydrothromboxane$_{B2}$ excretion.

1. Introduction

Cigarette smoking is an important modifiable risk factors for cardiovascular diseases (CVD) such as myocardial infarction, sudden death and stroke [1–3]. For instance, women smokers of 25 or more cigarettes per day have a relative risk (RR) of 5.4 (95% CI: 3.0–10.4) for fatal coronary heart disease (CHD) and 5.8 (95% CI: 4.2-8.0) for nonfatal myocardial infarction in comparison to non-smokers [4] while in men, the RR for myocardial infarction (fatal and non-fatal) for smokers *vs.* non-smokers is 3.63 (95%CI: 3.03-4.35) [5]. After smoking cessation, the risks for cerebrovascular and ischemic heart disease reduce by 50% after 4.78 years (95%CI: 2.17–10.50) [6] and 4.40 years (95%CI: 3.26–5.95) [7] respectively.

Alternatives to cigarettes are being developed and marketed. These alternatives deliver nicotine but reduce the exposure to harmful chemicals and therefore have the potential to reduce the risk of smoking related diseases compared to continued smoking. As these products become available, it will be important to provide consumers accurate information about the potential risk reduction. In the absence of long term epidemiological studies, the evaluation of risk modification through the use of products substituting combustible tobacco products may not be timely enough to address the public health opportunity these new products may offer. Thus, the study of clinical risk endpoints has become an integral component of PMI's assessment of how the reduction of toxicants in the inhaled aerosol by the consumer translates into a proxy of smoking-related disease.

Candidate endpoints of risk should be involved in biological pathways known to be affected by smoking, such as the in inflammatory response or plaque formation on arterial walls [8,9]. One of the biomarkers highlighted in the CVD and smoking-related disease literature is thromboxane, which is reported as a mediator involved in the pathogenesis of cardiovascular diseases [10]. Smoking has been associated with enhanced thromboxane A2 release by platelets in healthy individuals [11] and several studies have assessed the levels of thromboxane A2 in the plasma of smokers compared to non-smokers [12,13]. As well, the excretion of the two major urinary metabolites of thromboxane A2, namely 2,3-dinor-thromboxane$_{B2}$ [1,14] and 11-

* Corresponding author.
E-mail address: angela.vanderplas@pmi.com (A. van der Plas).

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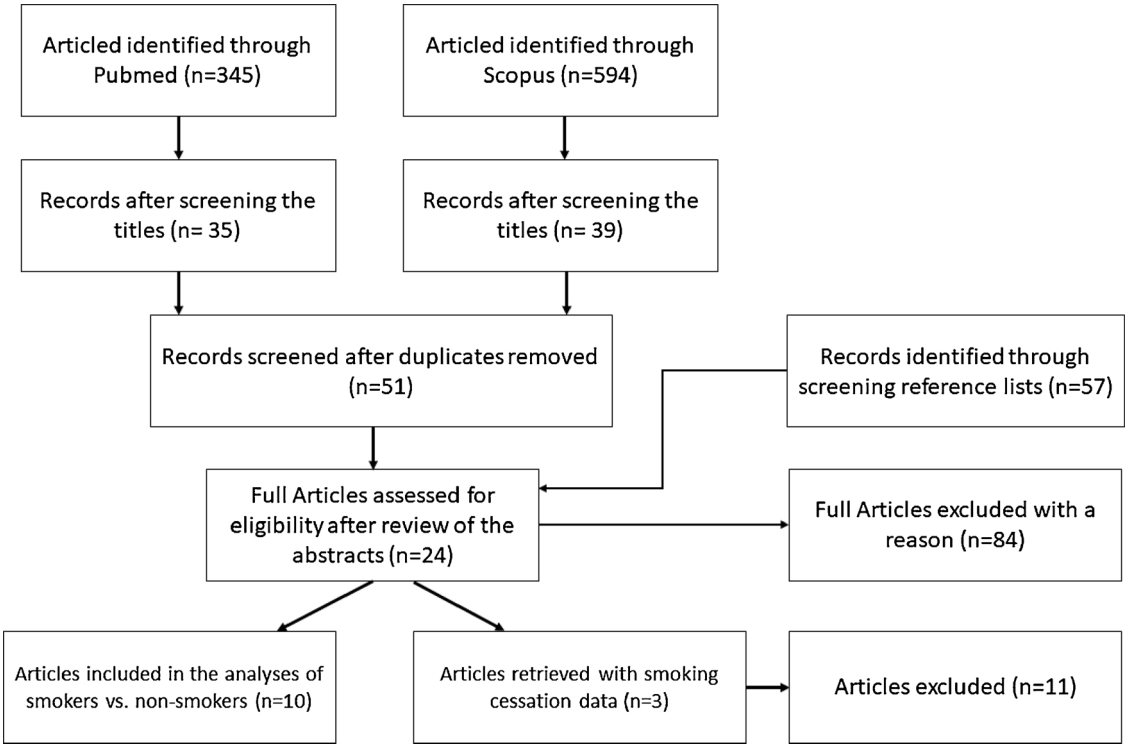

Fig. 1. Flow diagram – article retrieval process.

dehydro-thromboxane$_{B2}$ (TXB2)[1] [1] have been studied. Researchers have also assessed the effect of smoking cessation [15] on urinary TXB2 levels, where the data show that as early as three days after smoking cessation (without nicotine substitution), the TXB2 levels were lowered to levels of about 75% (p-value < 0.01) of the baseline values, and after 14 days, the levels were reduced to 50% (p-value < 0.01) of the baseline values.

The aim of this research was to assess the association of smoking status and urinary levels of TXB2 by reviewing and analysing the published available literature on: a) urinary TXB2 levels in smokers *vs*. non-smokers and b) the influence of smoking cessation on urinary TXB2 levels.

2. Methods

Medline searches were performed through PubMed and additionally in the SCOPUS database, for publications that evaluated the relationship between smoking or smoking cessation and urinary TXB2 levels. The final search was performed on March 9th 2018. The following query was used in PubMed: ("thromboxanes"[MeSH Terms] OR "thromboxanes"[All Fields] OR "thromboxane"[All Fields]) AND (("smoking"[MeSH Terms] OR "smoking"[All Fields]) OR ("tobacco"[MeSH Terms] OR "tobacco"[All Fields] OR "tobacco products"[MeSH Terms] OR ("tobacco"[All Fields] AND "products"[All Fields]) OR "tobacco products"[All Fields]) OR cessation[All Fields] OR quitting[All Fields]). In SCOPUS the following query was used: Thromboxane AND (smoking OR tobacco OR cessation OR quitting).

Retrieval of articles was limited to those written in English and considering human populations. To verify that all available publications were retrieved, the reference lists of the publications obtained through the original search were reviewed to identify any additional citation.

2.1. Study selection

The following criteria were used for including/excluding publications from the review:

a) Inclusion Criteria:
b) Case control, cross-sectional, cohort or interventional studies such as randomized controlled trials
c) Adult healthy human populations
d) Measurements of TXB2 by exposure with the following measures available: mean values by group, standard deviation (SD) or standard error (SE) (of the mean), sample size per group or with enough information to allow for the calculation of mean and SD
e) Studies published from 1970 until March 9th 2018
f) Exclusion Criteria:
g) Review articles, case reports or editorials
h) Studies with incomplete data
i) Studies where data had been re-used in a more recent study
j) Studies including diseased populations

2.2. Data extraction

Two researchers extracted data independently, discussed any disagreements and reached consensus on all items. The following information was extracted from each study: the first author's name, year of publication, study design and population characteristics, number of participants per group, mean, standard deviation (SD) or standard error (SE). Not all articles reported the measurements in the same units, so only publications where the values could be transformed to either pg/mg or μg/24-h were used. Transformation from median and range values was performed according to the calculations postulated by Hozo et al. [16].

2.3. Statistical analysis

Pooled means levels of urinary TXB2 by exposure group (smokers and non-smokers) were calculated by weighting the individual studies by their inverse pooled variance. To quantify the effects of smoking and smoking cessation on TXB2, pooled mean differences between smokers and non-smokers and 95% confidence intervals (95% CIs) were calculated using the fixed-effects model in Review Manager version 5.0 (Cochrane Collaboration, Oxford, UK). The degree of heterogeneity between the study results was tested by the inconsistency statistic (I^2).

[1] TXB2 = 11-dehydrothromboxane$_{b2}$.

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