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Blood carboxyhaemoglobin, plasma thiocyanate, and cigarette consumption: implications for epidemiological studies in smokers

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Abstract

Carboxyhaemoglobin and plasma thiocyanate concentrations were found to be significantly correlated with self-reported daily cigarette consumption in 360 smokers ($r=0.416$ and 0·412 respectively; $p<0.001$). The extent to which inhalation patterns affected the intake of cigarette smoke constituents was determined from the partial correlation between carboxyhaemoglobin and plasma thiocyanate concentrations after the number of cigarettes smoked per day had been allowed for ($r=0.48$). Thus 23% of the variation in carboxyhaemoglobin and thiocyanate concentrations was accounted for by the way a cigarette was smoked and a further 21% by the number smoked a day. Furthermore, the relation between carboxyhaemoglobin or plasma thiocyanate and daily cigarette consumption was not linear but reached an asymptote at consumption rates above 25 cigarettes a day.

These results suggest that by itself daily cigarette consumption will not identify those smokers most at risk and will also underestimate the dose-response relationship between smoking and selected diseases.

Introduction

It is generally accepted that the health risks associated with smoking increase in proportion to the number of cigarettes smoked a day. This presupposes that daily cigarette consumption is an adequate index of exposure to the toxic agents in tobacco smoke. Consumption may, however, be a poor measure of dose since smokers can vary their intake of smoke in other ways—by regulating the length and depth of inhalation or by the number and size of puffs.[1] Will a true estimate of the hazards of smoking then be provided by epidemiological studies which use daily cigarette consumption to determine exposure, or does a more accurate assessment need objective measures of tobacco smoke intake?

We have measured blood carboxyhaemoglobin and plasma thiocyanate concentrations in cigarette smokers in the course of other smoking-related studies. This has provided us with data to examine the relation between dose and cigarette consumption.

Subjects and methods

The subjects studied were all healthy volunteers and were either non-smoking or smoking members of staff at St Bartholomew's Hospital or smokers attending the Maudsley Hospital. There were 360 smokers (178 men and 182 women) and 79 non-smokers (51 men and 28 women). Venous blood was taken from each subject, usually in the late morning or afternoon, for the estimation of carboxyhaemoglobin and plasma thiocyanate. Carboxyhaemoglobin concentrations were determined with an IL282 CO-Oximeter[2] and plasma thiocyanate by an automated modification of the Aldridge technique.[3] These procedures have been described more fully elsewhere.[4]

Results

The smokers were subdivided into six classes on the basis of their daily cigarette consumption. The class intervals chosen allowed for digit bias in reporting daily consumption; 49% of our subjects recorded numbers as 10 or multiples thereof. Details of the number of subjects, average cigarette consumption, and mean (± SEM) carboxyhaemoglobin or plasma thiocyanate concentrations in each smoking class and in non-smokers are shown in fig 1. The significance of the differences in mean carboxyhaemoglobin or plasma thiocyanate concentrations between adjacent classes, using the Mann-Whitney U test, is also given. The biochemical measures each showed an asymptotic relationship with daily cigarette consumption. Initially the concentrations of these compounds rose rapidly and then reached a plateau at consumption rates above 25 cigarettes a day. The increases in the mean concentrations of carboxyhaemoglobin were relatively greater than those for plasma thiocyanate, shown by the appropriate selection of scales in fig 1.

The ranges of carboxyhaemoglobin and plasma thiocyanate concentrations within the six smoking classes are shown in fig 2. The separation between the cumulative distribution curves was distinct

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in the lower consumption groups but they were much closer to one another in the higher consumption groups. This further emphasised the asymptotic relationship between the measures and confirmed that daily consumption alone was not an adequate predictor of carboxyhaemoglobin or plasma thiocyanate concentrations. We have previously established[4] that 1·6% carboxyhaemoglobin and 73·0 μmol/l plasma thiocyanate are the best cut-off points for discriminating between smokers and non-smokers in our laboratory. The percentages of subjects with concentrations below these values are also indicated in fig 2.

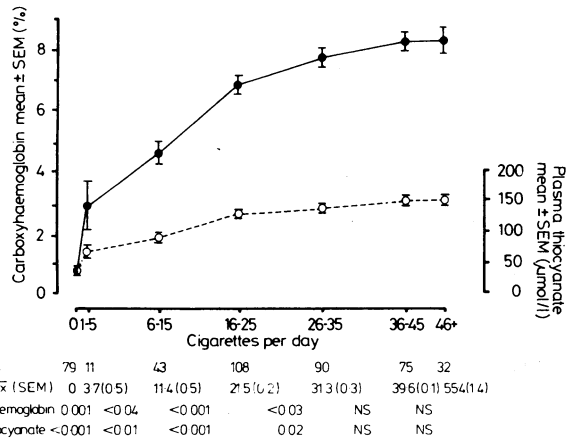

FIG 1—Mean blood carboxyhaemoglobin and plasma thiocyanate concentrations in non-smokers and six smoking classes. The chosen carboxyhaemoglobin and plasma thiocyanate scales emphasise the relative increases in their respective concentrations. The number in each class together with the mean daily cigarette consumption and the significance of the differences in carboxyhaemoglobin and plasma thiocyanate concentrations between neighbouring classes are also shown.

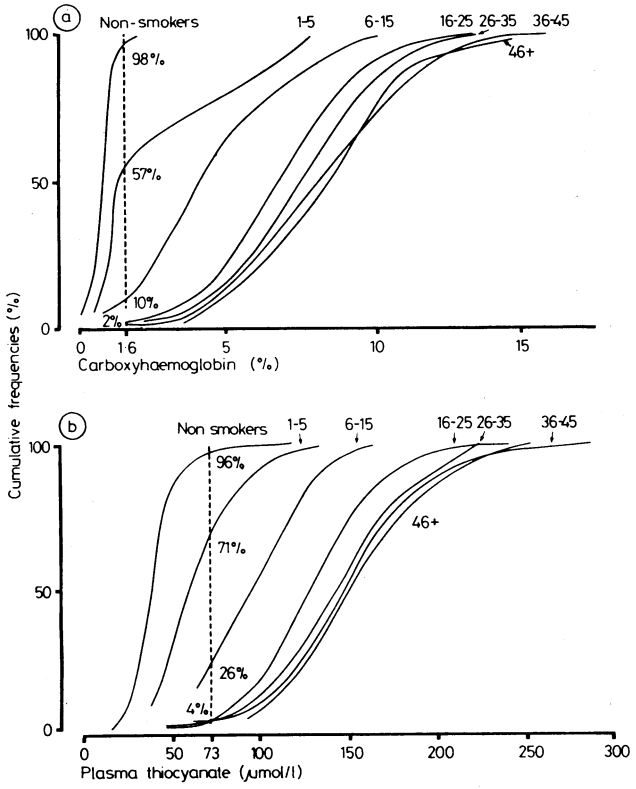

FIG 2—Cumulative frequency curves for (*a*) carboxyhaemoglobin and (*b*) plasma thiocyanate concentrations in each smoking category. The dashed lines at 1·6% carboxyhaemoglobin and 73 μmol/l plasma thiocyanate are the cut-off points for separating smokers from non-smokers. The percentage of subjects in each category who had non-smokers' concentrations, presumably because they were non-inhalers, are also shown.

The linear regression of carboxyhaemoglobin or plasma thiocyanate concentrations with daily cigarette consumption produced significant positive correlations in both instances (table I). Since the relationships between these variables were asymptotic, linear regression would have underestimated the true correlation. The data were made more nearly linear when logarithmically transformed, and as expected the correlation between log daily consumption and the biochemical measures was more positive. Carboxyhaemoglobin and plasma thiocyanate concentrations were better correlated with each other than with daily cigarette consumption.

Female smokers had significantly higher mean carboxyhaemoglobin and plasma thiocyanate concentrations than male smokers ($p < 0·001$), although there was no significant difference ($p > 0·5$) in cigarette consumption between the sexes (table II).

TABLE I—*Pearson correlations of carboxyhaemoglobin and plasma thiocyanate concentrations with daily cigarette consumption*

	Carboxyhaemoglobin concentration	Plasma thiocyanate concentration
Cigarettes per day	0·42	0·41
Log cigarettes per day	0·47	0·46
Plasma thiocyanate concentration	0·60	

TABLE II—*Mean (± SEM) cigarette consumption, carboxyhaemoglobin, and plasma thiocyanate concentrations in men and women*

	Men (n = 178)	Women (n = 181)	Significance of difference
Cigarettes per day	28·8 (1·1)	29·6 (0·9)	NS
Carboxyhaemoglobin (%)	6·6 (0·2)	7·5 (0·2)	p = 0·001
Plasma thiocyanate concentration (μmol/l)	124·3 (3·1)	147·4 (3·4)	p < 0·001

NS = Not significant; SEM = Standard error of the mean.

Discussion

Carbon monoxide and hydrogen cyanide (which is metabolised to thiocyanate) are both constituents of cigarette smoke which could contribute to the health hazards of smoking.[5] If a direct dose-response relationship between the concentrations of these toxins and a disease outcome exists it could be asked how adequately would daily cigarette consumption, the most commonly used measure of dose, estimate this association. In this study daily consumption accounted for about 21% of the variation in carboxyhaemoglobin or plasma thiocyanate concentrations (table I). It would, therefore, show only a weak positive correlation with diseases related to carboxyhaemoglobin or plasma thiocyanate concentrations. Epidemiological studies using daily cigarette consumption would thus underestimate the true risks from smoking.

In non-smokers the correlation between carboxyhaemoglobin and plasma thiocyanate concentrations was 0·05 but in smokers, after daily cigarette consumption had been allowed for, the partial correlation between them was 0·48. This positive correlation can arise only because both these compounds are derived from inhaled cigarette smoke. This suggests that a further 23% of the variation in the blood concentrations of these substances may be explained by the smokers' puffing and inhalation habits. An American study of male smokers[6] obtained correlations between daily cigarette consumption, end-expired carbon monoxide, and plasma thiocyanate concentrations similar to those that we report. The American study also showed that the conventional questionnaire estimates of dosage, such as depth of inhalation and the amount of each cigarette smoked, did not contribute significantly to the multiple regression of plasma thiocyanate and carbon monoxide. Together with our findings, this supports the view that smokers are unable to report accurately their inhalation habits. Thus a factor equally as important as daily cigarette consumption is usually ignored in many epidemiological studies. The remaining variability in

carboxyhaemoglobin or plasma thiocyanate concentrations, which is not explained by the factors above, may be due to differences in carbon monoxide or hydrogen cyanide yields of cigarettes, excretion, and environmental or nutritional factors.

The expectation that the risks of smoking increase in proportion to daily cigarette consumption would, according to our data, be met only for those smoking up to 25 cigarettes a day. Above this number there was no significant difference in mean carboxyhaemoglobin or plasma thiocyanate concentrations between the various smoking classes (fig 1). It is relevant in this respect that two recent studies have found that the incidence of myocardial infarction in smokers reaches a plateau at about one packet of cigarettes a day.[7 8]

Many smokers achieved a high carboxyhaemoglobin or plasma thiocyanate concentration despite smoking few cigarettes. In contrast, some smokers with high cigarette consumption had low carboxyhaemoglobin or plasma thiocyanate concentrations. Figure 2 shows that 2-4% of subjects smoking 26-35 cigarettes a day are likely to have the same risk as non-smokers, while a proportion of those smoking 1-5 cigarettes a day may be at greater risk than others smoking 10 times as many cigarettes. Daily cigarette consumption will thus indicate the potential risk associated with a certain rate of smoking, but biochemical tests would actually identify those people at highest risk. Since many smokers rationalise their smoking habits by denying the relevance of impersonal health statistics to their own lives ("I don't smoke enough to get the diseases smoking is supposed to cause" or "It won't happen to me"),[9] the measurement of individual exposure could be an important factor in modifying smoking behaviour.

Our population was unusual in that mean cigarette consumption was not significantly different in men and women (table II), whereas most studies report a higher rate of smoking by men.[10] The difference in mean carboxyhaemoglobin and plasma thiocyanate concentrations between the sexes requires explanation. Russell *et al*[11] also found that among smokers women had higher mean carboxyhaemoglobin concentrations than men, but this difference became insignificant when smokers of plain cigarettes (mostly men) were excluded from the analysis. Smokers of unventilated filter cigarettes have higher carboxyhaemoglobin concentrations than plain cigarette smokers.[12] While we do not have a record of the types of cigarettes smoked by our subjects, this seems the most likely explanation of our findings. The observed difference in plasma thiocyanate concentrations between the sexes has not previously been reported.

In conclusion, our data suggest that the measurement of either carboxyhaemoglobin or plasma thiocyanate concentrations is superior to self-reported cigarette consumption as an index of exposure to tobacco smoke. Prospective studies of smoking-related diseases should, therefore, incorporate a biochemical estimation of smoke intake. The choice of index compound will depend on the objectives of the study. Thus carboxyhaemoglobin will not be appropriate in a study of oral cancer in primary pipe or cigar smokers. These smokers do not inhale smoke into the lungs and so have low carboxyhaemoglobin concentrations.[13] For cigarette smokers, however, the easiest single measurement presently available, provided care is taken over the timing of the sample,[14] is the estimation of carbon monoxide in end-expired air.[2] Furthermore, it is encouraging that good correlations have been reported between carboxyhaemoglobin and blood nicotine concentrations in humans[11] ($r=0{\cdot}53$) and carboxyhaemoglobin and tar deposition in the lower respiratory tract in animals[15] ($r=0{\cdot}795$). Alveolar carbon monoxide or carboxyhaemoglobin may, therefore, also be used to indicate the relative exposure to other compounds in tobacco smoke. A limitation of biochemical markers, however, is that they reflect current smoking practices rather than those of previous years during which pathological changes may have started to take place.

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OF A SCIRRHUS AND CANCER.

A SCIRRHUS is a hard indolent tumour ſeated in ſome of the glands; as the breaſts, the arm-pits, &c. If the tumour becomes large, unequal, of a livid, blackiſh or leaden colour, and is attended with violent pain, it gets the name of an *occult cancer*. When the ſkin is broken, and a *ſanies* or ichorous matter of an abominably fœtid ſmell is diſcharged from the ſore, it is called an open or ulcerated cancer. Perſons after the age of 45, particularly women, and thoſe who lead an indolent ſedentary life, are moſt ſubject to this diſeaſe.

CAUSES.—This diſeaſe is often owing to ſuppreſſed evacuations; hence it proves ſo frequently fatal to women of a groſs habit, particularly old maids and widows, about the time when the menſtrual flux ceaſes. It may likewiſe be occaſioned by exceſſive grief, fear, anger, religious melancholy, or any of the depreſſing paſſions. Hence the unfortunate, the choleric, and thoſe perſons who devote themſelves to a religious life in convents or monaſteries, are often afflicted with it. It may alſo be occaſioned by the long-continued uſe of food that is too hard of digeſtion, or of an acrid nature; by barrenneſs; celibacy; indolence; cold; blows; friction; preſſure; or the like. Women often ſuffer from the laſt of theſe by means of their ſtays, which ſqueeze and compreſs their breaſt ſo as to occaſion great miſchief. Sometimes the diſeaſe is owing to an hereditary diſpoſition.

(Buchan's *Domestic Medicine*, 1786.)