Searching for Smokers: A Comparison of Carboxyhemoglobin, Thiocyanate and Cotinine As Screening Tests

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Burgeoning evidence of the formidable mortality consequences of cigarette smoking has motivated life insurers to offer lower premiums to non-smokers. With widely-advertised non-smoker discounts also available on property-casualty and health insurance products, the alert consumer is now aware of the economic advantage of being a non-user of cigarettes, even if only temporarily (i.e., when the agent is filling out the application).

The purpose of this paper is to evaluate three substances which can be used as screening tests to detect tobacco use: carboxyhemoglobin, thiocyanate, and cotinine. The advantages and disadvantages of each will be reviewed, in part to ascertain if there is a clearly preferable test for risk selection purposes.

Carboxyhemoglobin (COHb)
Carbon monoxide (CO) is present in tobacco smoke and when it is inhaled, it binds with hemoglobin to form carboxyhemoglobin (COHb). Because CO has a hemoglobin-binding affinity 210 times greater than oxygen, tobacco smoke inhalation readily leads to COHb formation.

Carboxyhemoglobin impairs the transport of oxygen to tissues. In sufficient quantity, it will produce a functional anemia. High COHb levels also increase cardiac oxygen demand, inducing acute myocardial hypoxia in persons with atherosclerotic obstructive disease.[1]

The main sources of COHb are tobacco smoke and gasoline engine exhaust fumes. It is common for non-smokers to have 0.5% to 2.0% CO hemoglobin saturation.[2] The 1979 Surgeon General's Report on Smoking and Health revealed CO saturation levels up to 3.7% in non-smokers in industrial areas.[3] A 1981 study in Environmental Research compared COHb in smokers and non-smokers in two Ohio communities with different levels of pollution. In industrialized Cleveland, mean COHb in male non-smokers was more than 50% higher than in non-smoking men from Elyria.[4]

A study by Cohen and Bartsch contrasted COHb in smokers and non-smokers. Smokers had a mean value of 4.5% while non-smokers averaged just 1.1%.[5] The most likely explanation for high readings in non-smokers is exposure to engine exhaust. Taxi drivers, traffic police and garage workers, for example, have been shown to have saturations up to 10%.[6]

COHb varies throughout the day and is influenced by recent smoking. A Swedish study revealed the average level in cigarette smokers rose as consumption increased. Fourteen (14) of 33 light smokers (less than 10 cigarettes per day) averaged under 1% COHb saturation. Only 12 of 244 heavier users (10 or more per day) had an equally low reading. In the same report, virtually all non-smokers had COHb ranging from "undetectable" to 0.99% saturation.[7]

Several studies have shown that cigar smokers who inhale have higher COHb than cigarette smokers and other tobacco users.[8] Inhalation is critical, as illustrated when Goldman and his colleagues found an average COHb of 13.8% in inhaling cigar smokers as compared to 2.1% in non-inhaling users. The increase in saturation among inhaling pipe smokers was almost four-fold, again as compared to non-inhalers. Interestingly, pipe inhalers have almost the same average reading as cigarette inhalers (5.0%, compared to 5.6%).[9]

There are three drawbacks to COHb: brief half-life in the bloodstream, wide variation in readings and limited availability. The problem of the short half-life is clearly the biggest obstacle.

A 1978 paper reported that COHb levels normalize following 24 hours of cigarette abstinence.[10] In another article, when five heavy smokers quit for 36 hours, mean COHb declined from 11.8% to 2.9%.[11] It is realistic to assume that some insurance buyers will readily hold off smoking for a day or two if forewarned of possible screening tests. Therefore, the ra-

pid clearance of COHb renders this test unsuitable for use as a screening tool.

Should COHb be used as a "fail-safe" mechanism, to be ordered by an underwriter when a urine test for nicotine/cotinine is positive but the insured complains that he does not smoke? Two factors make this use of COHb impractical. First, researchers have found rather dramatic variations in readings among individuals with the same cigarette intake.[12] This finding, together with the limited number of facilities which can perform COHb tests, limits the usefulness of carboxyhemoglobin.

Thiocyanate

Thiocyanate is an end product of the detoxification of hydrogen cyanide. It accumulates in the body, inhibiting cellular respiration.[13]

Several investigators have shown that blood, urine and saliva concentrations of thiocyanate are higher in tobacco smokers than in non-smokers. For example, a 1981 Ontario study revealed an average level of 86 units in smokers as compared to 22 units in non-smokers.[14] West German investigators found the mean serum thiocyanate in cigarette smokers was 141 units, and it was just 51 units in non-smokers.[15] In that same study, 42% of subjects who smoked 5-10 cigarettes per day and 11% who used up to 20 cigarettes daily had a reading of 100 or less, effectively indistinguishable from non-smokers.

The biggest advantage to thiocyanate is its half-life, estimated to be 14 days.[16] Thiocyanate should be detectable despite as much as a week of cigarette avoidance. Thiocyanate has also been shown to have a higher sensitivity than carboxyhemoglobin (93% vs. 83%) for detecting recent smoking.[17]

Were it not for one weakness, thiocyanate might be "the test of choice" for our purposes. However, the weakness, which is a high incidence of false positive results, undermines the value of thiocyanate.

The Lab Manual from Metpath Laboratories cautions that salicylates cause a positive test. Vogt and his colleagues report false positives in individuals who have recently consumed such foodstuffs as cabbage, broccoli, garlic, horseradish, radishes, mustard and almonds. Vegetarians have elevated thiocyanate, as do individuals with industrial exposure to thiocyanate (e.g., electroplaters, precious metal refiners).[18] Haley, Axelrad and Tilton found that "diets enriched in certain foods can produce thiocyanate levels as high as those found in habitual smokers"[19]. When Densen and his colleagues evaluated urine, serum and saliva thiocyanate, they had to ask volunteers to refrain from eating a long list of foods.[20] Insurance companies have little inclination and even less practical capacity to record or restrict the eating habits of applicants. Hence, we are on shaky ground relying solely on thiocyanate test results.

Might we consider thiocyanate tests in disputed cases, where a urine specimen is positive for nicotine/cotinine but the insured disclaims tobacco use? The long half-life of thiocyanate makes this tempting, notwithstanding the fact that light smokers and/or shallow inhalers may have readings in the non-smoking range.[21]

Cotinine

Cotinine is a major metabolite of nicotine. Unlike nicotine, which is quickly excreted from the body, cotinine stays long enough to discourage anti-selection. When Hill and his co-workers compared carboxyhemoglobin, thiocyanate and cotinine, they found cotinine remained "fairly constant in individuals who smoke consistently". In contrast, COHb and thiocyanate were distorted by both physical activity and diet.[22]

British investigators who were seeking to identify clandestine smoking in their post-infarction patients found that by measuring cotinine, they could identify smokers concealing the habit.[23] An Australian study compared COHb, thiocyanate and cotinine. At a specificity of 95%, the sensitivity of cotinine was higher (98%) than either COHb (94%) or thiocyanate (80%). The authors concluded that cotinine was "the best single biochemical test with which to distinguish smokers from non-smokers in clinical and epidemiological studies".[24]

Haley and her co-workers at the American Health Foundation assessed cotinine and thiocyanate from both plasma and saliva. Non-smokers had no detectable cotinine in either medium. Abundant thiocyanate, on the other hand, was found in many non-smokers. The authors decided that thiocyanate provided a "less clear-cut answer" than cotinine to smoking status. They observed that "in both plasma and saliva, cotinine analysis could distinguish between smokers and non-smokers with a higher degree of accuracy".[25] Several other researchers have also found cotinine to be more specific and more reliable than thiocyanate in this context.[26]

A Japanese study published recently in the New England Journal of Medicine indirectly

questioned the reliability of cotinine when it showed that non-smokers who lived or worked in proximity to smokers had significant urine cotinine levels. Reporting findings in micrograms of cotinine per milligram of creatinine, they showed how heavily exposed non-smokers had an average cotinine of 1.56 units, compared to the average smoker who had 8.57 units.[27]

The findings in this study should have no important impact on nicotine/cotinine tests as we use them in risk selection. In a letter to The Lancet in January, 1984, Wald and his colleagues acknowledged they found cotinine in the urine of passive smokers but the break-off between smokers and non-smokers was dramatic. Reporting results in nanograms per milliliter, they recorded an average cotinine of 6 units in exposed non-smokers and 2 units in unexposed non-smokers. Cigarette smokers had an average of 1,645 units(!)[28]

Pojer and his co-workers looked at plasma cotinine in non-smokers who had a heavy passive smoke intake. They reported the average cotinine in smokers was 19 times higher than in "exposed" non-smokers.[29]

At Northwestern Mutual Life, we require routine nicotine/cotinine urine tests at certain age and amount thresholds. We believe we have elimiminated the problem posed by passive smoking by adjusting our starting point for a positive test. Whereas our laboratory vendor reports values of 0.5 units or higher as positive, we do not consider a test to be indicative of smoking until the actual reading is 1.0 units or higher. We are confident that, at this threshold, we have eliminated all possible false positives due to passive smoking.

SUMMARY

The problem of screening for concealed smoking among applicants is formidable, in part because there is as yet no cigarette-specific test. Carboxyhemoglobin, thiocyanate and cotinine are compromised, if you will, because pipe smoking, cigar smoking and other forms of tobacco use will produce positive results. This dilemma is minimized by wording the Smoking Question on the application so as to elicit details of all forms of tobacco use. Nonetheless, we do remain vulnerable to those who claim to smoke pipes or cigars solely to mask the real meaning of nicotine/cotinine in their urine.

Carboxyhemoglobin is useless because of its rapid excretion. Nicotine is also compromised on these grounds, but its metabolite, cotinine, is not. Cotinine is superior to thiocyanate as a screening test because it is not subject to false positive results from salicylates and foodstuffs. Therefore, cotinine is the best choice for life insurers to measure when screening for smoking. Urine cotinine tests are preferable to blood or saliva studies because they can be secured at modest cost from the major laboratories serving our industry. Blood and saliva continine tests are difficult to obtain but should theoretically be equally valid for screening purposes.

If we are challenged on the results of a urine nicotine/cotinine test by an applicant who disclaims tobacco use, a practical "fail-safe" mechanism would be to offer to review the results of a blood test for cotinine or thiocyanate. Major laboratories can perform either on request. The average cost is $40 - $60, which is reasonable if it resolves a challenge on the smoking status of an insured seeking a large policy.

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