Usefulness of Sweat Testing for the Detection of Cannabis Smoke

Several reports have demonstrated that sweat is a suitable alternative biological matrix for monitoring recent drug use *(1, 2)*. This is based on the assumption that, in the context of the absorption/distribution/metabolism/excretion (ADME) cycle of drugs, a small but sufficient fraction of a drug is excreted in sweat and can be tested. The passage of lipid-soluble compounds from blood to other fluids or matrices is regulated by the substance's pK_a and by the pH of the other fluids or matices. A modified version of the Henderson–Hasselbach equation, which uses the pK_a and the pH, allows theoretical calculation of the fluid-to-plasma concentration ratio (F/P ratio) *(3)*. Drugs are generally incorporated into sweat by passive diffusion because of a concentration gradient in which only the free fraction of drug (unbound to proteins) diffuses through lipid membranes from plasma to sweat. Furthermore, because under normal conditions sweat, with a mean pH of 6.3, is more acidic than blood, basic drugs tend to accumulate in sweat.

Two approaches are currently used in testing for drugs in sweat. The first is aimed at detection of recent use of drugs (<24 h) and involves only collection of sweat at a point in time. An immunochromatographic test of the sample then provides a qualitative result *(4)*, or drugs in sweat collected on a cotton wipe can be extracted and subjected to confirmatory analysis *(5)*. This approach is mainly oriented to identify individuals who are under the influence of drugs. The second approach is based on patch technology and allows monitoring of illicit drug use for time windows wider than those provided by urine testing. This is because the patches can be worn for up to 1 week. Drugs accumulate in the collection device, and little or no drug degradation seems to occur during this time interval *(1)*. Patch technology is used mainly for the follow-up of drug addicts under treatment to verify abstinence. Both approaches benefit from low invasivity and pose fewer ethical problems for sample collection than does blood or urine testing.

Until recently, the use of sweat for drug testing has been hampered by difficulties in sample recovery and by the limited sensitivities of analytical methods *(6)*. Success in sweat testing for several drugs of abuse *(4, 7–13)* has been accomplished because of substantial advances in sample collection and improved accuracy of measurement methods. An important advance is the development of the sweat patch technology *(14)*, used by Saito et al. *(15)* to detect Δ^9-tetrahydrocannabinol (THC) in sweat, as reported in this issue of *Clinical Chemistry*. Sweat patches applied to the skin allow oxygen, carbon dioxide, and water vapor to escape, whereas the nonvolatile components, including drugs of abuse, are retained in the absorbent pad *(8)*. Further extraction of drugs from the patch is required, but analyses are relatively easy because the chemical composition of sweat is simple compared with that of blood or urine. A variety of drugs of abuse, including opiates, cocaine, and amphetamines, have been detected in sweat by use of the patch technology *(4, 8, 9, 12, 13)*, but little information is available concerning the presence of cannabinoids in sweat.

The detection of THC, the psychoactive component of cannabis (e.g., marijuana smoke and hashish), in sweat was first reported in 1990 *(16)* and subsequently found in sweat wipes from intoxicated drivers *(5)*. In contrast to the majority of drugs of abuse, which are weak bases and tend to concentrate in biological matrices more acidic than plasma, THC is a neutral molecule and hence its diffusion is expected to be slower. Indeed, THC was found in the low ng/patch range, and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol, the principal acidic urinary metabolite, has been never detected in sweat *(17)*. Mandatory guidelines for federal workplace drug testing programs that were recently revised by the Substance Abuse and Mental Health Services Administration (SAMHSA) *(18)* address sweat testing for marijuana use. The guidelines require finding of marijuana metabolites at an initial cutoff concentration of 1.5 ng/2.5 mL of eluate (without specifying the quantity of specimen to be collected) and a confirmatory cutoff concentration of 0.5 ng/2.5 mL of eluate for THC.

In this issue of *Clinical Chemistry*, Saito et al. *(15)* describe the validation of a gas chromatographic–negative ion chemical ionization mass spectrometric method to detect THC in patches to which THC was added. The assay was initially developed based on an early confirmatory cutoff proposed by SAMHSA in December 2003 of 1 ng/patch for THC in sweat. Nonetheless, with limits of detection (LOD) and quantification (LOQ) of 0.2 ng and 0.4 ng per 2 mL of eluate, the assay has the potential of meeting the newly issued cutoff concentration. Furthermore, the authors investigated the recovery of THC from the collection pad. It appears that a substantial fraction of the drug remains bound to the pad, something expected taking into account the lipophilic nature of the drug and its avidity to glass and plastic surfaces *(19)*.

Although the availability of analytical methods meeting administrative standards is a further step for the routine detection of THC consumption by analysis of sweat, several issues require thorough investigation as they may limit the application of THC sweat testing. Three issues must be considered: environmental skin contamination, drug absorption/loss through patch membrane, and drug reabsorption from patches.

Cannabis is the illicit drug with the highest worldwide consumption prevalence and the highest rate of positive findings in workplace drug testing. Consequently, cannabis was the first drug for which excuses were provided to explain a positive test result, an issue that was recently the subject of an Editorial in this journal *(20)*. Sweat patches are sealed to the skin and were designed to exclude environmental contamination. In an in vitro study, Kidwell and Smith *(21)* showed that several drugs of abuse applied directly to the skin of drug-free individuals may

persist there for several days. Neither normal hygiene nor cleaning procedures recommended before application of the sweat patch completely remove drugs deposited on skin. Thus, it might be argued that environmental contamination before patch application is a possible occurrence. Nevertheless, THC was less likely to persist on skin *(22)*. Studies are needed of drug-free individuals exposed to environments heavily contaminated with cannabis smoke.

Some reports suggest that the patch membrane is permeable not only to gases and water vapor but, to a certain extent, to drugs *(21, 23)*. Drugs of abuse applied on the surface of patch membrane can be absorbed, and drugs excreted in sweat may diffuse through the membrane to the outer environment. These findings suggest that membranes are more permeable than expected, although for all drugs studied, <15% of the total amount of drug present on the inner side of the membrane was able to diffuse to the outer side *(21, 23)*. To date, the permeability of patch membranes for THC has not been studied, and investigations on this issue should be also promoted.

Finally, several studies suggest that there is a time-dependent loss of drugs during patch wearing over time. The loss of drugs of abuse from skin patches limits one of the goals of sweat patch testing: cumulative drug detection. One of the most likely mechanisms involved in drug loss is reabsorption back into the skin. This phenomenon has recently been well characterized for two basic drugs, cocaine and 3,4-methylenedioxymethamphetamine (MDMA) *(4, 23)*. The rate of reabsorption for THC is unknown, but it could be important because the amount of drug excreted through skin is low. Whereas chronic heavy cannabis users would be easily detected, this may not be the case for recreational users, giving rise to false-negative results.

In conclusion, the report of Saito et al. *(15)* in this issue of *Clinical Chemistry* is a first relevant step for the routine detection of THC consumption through sweat testing. The stage is set for the next steps of experimental studies of environmental skin contamination and studies to characterize drug reabsorption from patches.

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Rafael de la Torre[1,2*]
Simona Pichini[3]

[1] Institut Municipal d'Investigació Mèdica (IMIM) and [2] Universitat Pompeu Fabra Barcelona, Spain

[3] Drug Research and Control Department Istituto Superiore di Sanità Rome, Italy

*Address correspondence to this author at: Institut Municipal d'Investigació Mèdica (IMIM), Doctor Aiguader 80, E-08003 Barcelona, Spain. Fax 34-932213237; e-mail rtorre@imim.es.

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