Gisela Skopp,[1] *Lucia Pötsch,*[2] *Hans-Peter Eser,*[3] *and Manfred R. Möller*[3]

Preliminary Practical Findings on Drug Monitoring by a Transcutaneous Collection Device

REFERENCE: Skopp G, Pötsch L, Eser H-P, Möller MR. Preliminary practical findings on drug monitoring by a transcutaneous collection device. J Forensic Sci 1996;41(6):933–937.

ABSTRACT: A noninvasive and nonocclusive skin patch (Sudormed™) was investigated for the systematic collection of drugs of abuse over a period of several days. First, the applicability and user friendliness were tested by volunteers. The permeability of the polyurethane dressing from the outside to the inside for an aqueous solution was shown by incubating the outside layer with Rhodamine B. No fluorescence could be detected in the cotton pad beneath. A single dose experiment using theophylline as a model compound showed that there was a delay in time before the substance could be determined in the pad. The drug content decreased with increasing time of patch application. When eight volunteers participating in a methadone treatment were monitored, the substitute drug could always be detected in the patch associated with a minor concentration of EDDP. Besides, in some of the patches investigated, indications for an abuse of cocaine and heroin were found. The so-called sweat patch appears to be a valuable tool in clinical and forensic toxicology, as it offers a longer and prospective surveillance period compared with blood and urine testing.

KEYWORDS: forensic science, forensic toxicology, transcutaneous collection device, sweat-patch testing, transcutaneous drug delivery, drug monitoring, drugs of abuse, methadone, theophylline

First observations on outward transcutaneous drug delivery date back to the 19th century. In 1852, Schottin (1) verified iodide and benzoic acid in perspiration fluid by an experiment on his own body. Seventy years later, the first forensic case was reported by Jansch (2) who detected crystals of Veronal™ in droplets formed on the skin surface of a corpse after the body's storage had been changed from cold to ambient temperature. In the following decades, a series of clinical studies were done to determine the identity and the variability of drug and metabolite excretion in sweat following administration of single doses in most of the cases. The presence of several drugs of abuse has been reported, including alcohol (3–6), amphetamines (7,8), cocaine (9–12), opiates such as heroin and morphine (10,11,13), methadone (14,15), and phencyclidine (16).

The sweat samples collected in the studies were mostly obtained by an occlusion bandage. However, Hartmann (17) observed that an occlusive patch generally affects skin moisture and skin pH. He found that the relative skin moisture increased and skin pH shifted from the acidic range (4.9) to the the neutral range (7.1) during a 3-day occlusion experiment of the forearm. In addition, the bacterial population of superhydrated skin is altered, and an increase occurs during occlusive conditions (18).

Investigations with stimulation of sweat production by pilocarpin and electric current were performed using a collection swab (19) or a filter paper wrapped in plastic foil (10). Other working groups collected perspiration by rubbing the skin with a piece of gauze or towel at a temperature of 50°C (13). A self-produced transcutaneous collection device consisting of an adhesive-tape-encased agarose gel containing activated carbon as a binding agent was presented by Conner et al. (20).

Although numerous drugs of abuse have been detected, the application of transcutaneous drug delivery in forensic and criminal cases is rare. One of the reasons is that, up to 1993, there was no simple or standardized solution to the problem of capturing sweat for the analysis of drugs of abuse nor for drug monitoring over a period of a few days. Previous studies (21,22) demonstrated that clothes worn next to the skin might be a potential material for drug analysis, but the problems of external contamination are obvious. The possibility of a contamination-free sample collection arrangement is supposed to be one of the essential requirements for the forensic application of sweat testing.

Nowadays, a commercial transcutaneous drug collection device is available (23). The patch consists of an acrylate adhesive layer on a thin transparent polyurethane film. This dressing is nonocclusive and allows moisture and volatile substances to pass through the patch outward from the skin. Perspiration is collected on a cellulose absorption pad in the center of the adhesive layer. A unique number is imprinted on each sterile patch to ensure the chain of custody.

A transcutaneous drug collection device may offer new possibilities for studying the compliance of patients under medical treatment or of patients participating in a rehabilitation program and also for monitoring additional drug intake over a certain period. In this preliminary study, the following aspects were under investigation:

(1) Applicability and user friendliness of the patches,
(2) Permeability of the dressing toward inside direction for aqueous solutions,
(3) Transcutaneous flux after a single dose application of theophylline, and
(4) Transcutaneous collection under steady-state conditions, thereby drug monitoring patients participating in a methadone treatment program.

[1]Institute of Legal Medicine, Ruprecht-Karls-University, Voßstr. 2, Heidelberg, Germany.
[2]Institute of Legal Medicine, Johannes-Gutenberg-University, Am Pulverturm 3, 55131 Mainz, Germany.
[3]Institute of Legal Medicine, University of the Saarland, 66421 Homburg, Germany.

Received for publication 4 Dec. 1995; revised manuscript received 8 Feb. and 29 March 1996; accepted for publication 1 April 1996.

Materials and Methods

Experimental Design

Applicability and User Friendliness—The skin was cleansed using 70% isopropanol before applying the patch. At the end of the experiments each of the volunteers reported on the impression of comfort or discomfort sensed while wearing the patches.

Permeability Towards Inside Direction for Aqueous Solutions—The patch was tested by incubating the polyurethane film with a Rhodamine B solution (1% in saline, pH 7.4) at ambient temperature overnight. The fluid was removed by soaking with filter paper. Then the film was opened with a scalpel and the cellulose pad inspected and viewed under ultraviolet light.

Single-Dose Test with Theophylline—The subjects were two healthy volunteers. Placement areas on the chest along the lower rib and lateral to the midline were cleansed with a 70% solution of isopropyl alcohol. Blanks were established by applying patches for 24 to 72 h before oral administration of theophylline (400 mg). After administration of theophylline, the transcutaneous collection devices were applied (n = 8/subjects). After time intervals of 12, 24, 48, and 72 h, two patches were removed, each symmetrically located on both sides of the chest.

A linear standard calibration curve was prepared by spiking unused cellulose pads with 100-, 200-, 500-, and 1000-ng theophylline in artificial sweat (24). A blank was also made. All investigations were performed twice, and all values are given as mean values. The cellulose pads of all transcutaneous collection devices were cut into small pieces. The snippets were gently agitated in 2 mL of methanol and were then removed by centrifugation. The supernatant was evaporated to dryness under nitrogen and the residue redissolved in 100 μL of the mobile phase. For high performance liquid chromatography (HPLC) analysis, 5 μL were injected. The limit of detection was 50-ng theophylline/patch.

Drug Monitoring Patients on Chronic Methadone Treatment—The subjects were eight volunteers participating in a rehabilitation program. Methadone as solution was taken once daily for a period of at least four weeks. The individual, constant doses were kept up during patch application. The height, the weight, and the daily doses of methadone were: A, 172 cm/68 kg/0.4 mg/kg; B, 171 cm/75 kg/1.2 mg/kg; C, 182 cm/85 kg/0.3 mg/kg; D, 183 cm/70 kg/1.0 mg/kg; F, 178 cm/69 kg/0.7 mg/kg; H, 176 cm/94 kg/1.1 mg/kg; I, 191 cm/83 kg/0.5 mg/kg; K, 165 cm/53 kg/0.4 mg/kg. Cleansing of the skin and placement areas were as described in three. One patch (n = 5/subjects) was removed after 2, 3, 4, 5, and 7 days.

The cellulose pads were removed from the adhesive layer and cut into small pieces. 2.5 mL of Soerensen buffer (pH 7.4) was added together with the internal standard substances (100 ng/50 μL). Extraction was performed in an ultrasound bath (10 min). The snippets were removed by centrifugation and shaken again in 2.5-mL Soerensen buffer. The extraction process was repeated twice. The pooled aqueous layers were extracted with solid phase extraction columns and eluted with 2-mL acetone/dichloromethane (3:1, v/v). The extracts were derivatized with pentafluoropropionic anhydride and pentafluoropropanol before GC/MS analysis. Quantification was done using the drug deuterated analogues as internal standards. Further analytical details were as given by Moeller et al. (24).

The samples were analyzed not only for methadone and its major metabolite EDDP (1,5-dimethyl-3,3-diphenyl-2-ethylidenepyrrolidine) but also for 6-acetylmorphine, morphine, codeine, dihydrocodeine, benzoylecgonine, and cocaine.

Chemicals and Reagents

The sweat patch specimen container was kindly supplied by Sudormed (Santa Ana, CA, USA). All solvents were of HPLC or analytical grade. The solid phase extraction columns were obtained from Macherey & Nagel (Düren, Germany). Rhodamine B, pentafluoropropionic anhydride and pentafluoropropanol were obtained from Aldrich-Chemie (Steinheim, Germany), 6-acetylmorphine, morphine, codeine, dihydrocodeine, cocaine, benzoylecgonine, methadone, EDDP, and the corresponding deuterated sample except for dihydrocodeine were purchased from Radian Corporation (Austin, TX). Deuterated dihydrocodeine was kindly contributed by G. Sticht (Institute of Legal Medicine, Köln, Germany).

Instrumentation

HPLC—Analysis was performed with a HP 1050 HPLC-system equipped with a diode array detector (Hewlett Packard, Waldbronn, Germany). Samples were eluted from a Lichrosphere reversed phase column, 125- by 3-mm (49- by 1.2-in.) I.D. (Merck, Darmstadt, Germany) with a mobile phase containing acetonitrile/methanol/water (3/2/2, v/v/v) at a flow rate of 0.5 mL/min at 35°C.

GC/MS—The following instruments were used: a HP 5890 II series gas chromatograph, a HP 5971 A mass selective detector, a 486 IBM-compatible personal computer equipped with a HP ChemStation B.02.04, a HP 7673 A automatic sampler (Hewlett Packard, Waldbronn, Germany). A HP-1 fused-silica capillary column was used for the analyses. The mass spectrometer was operated in the EI mode with an electron energy of 70 eV.

Results

Applicability and User Friendliness—Application of the patches was performed without any problems. When the patch was placed carefully and tightly, showering and swimming were possible as the interior pad did not become wet. Care should be taken, however, when wiping dry with a towel because the adhesive borders of the film are very sensitive to any rubbing or to skin movement. After hard exercise unnoticed by the volunteers (n = 2), some patches got lost. The application of numerous patches caused personal discomfort in five volunteers. A few persons (n = 3) got skin irritations such as itching, rubor, and swelling which disappeared within several hours after removal of the dressing. Reapplication of a formerly affixed patch was not successful. This was also the case if only one edge of the adhesive layer was lifted.

Permeability for Externally Applied Substances—The outside layers of the polyurethane film were highly fluorescence positive. But there was no visible contamination of the cellulose pad beneath the film after the incubation with the Rhodamine B solution. Even under ultraviolet light, fluorescence because of Rhodamine B contamination could not be detected in the pads.

Theophylline Experiment—The results of the single-dose experiment with theophylline are shown in Fig. 1. Theophylline could be detected in the 24-h pads or in the 48-h pads with a maximum concentration found 48 h after the intake of the drug substance. There was a corresponding decrease in the theophylline concentrations in the 72-h patches for the two subjects investigated.

Drug Monitoring During Methadone Treatment—The results of drug monitoring of the eight patients participating in a methadone treatment program are shown in Table 1. All patches tested positive for methadone and EDDP. After the third day of patch application period, no increase in drug or drug metabolite concentrations could be measured for any specimen. In all cases, the concentration of methadone exceeded the concentration of EDDP by several times. For example, after a patch wear period of four days, the ratio of methadone to EDDP ranged from 16 to 34 (mean value 27).

By GC/MS analysis, a consumption of drugs different from the substitute drug could be detected in the patch extracts. An example for abuse of heroin and cocaine is shown in Fig. 2. In patient K, the drug concentrations found on day five were a small fraction of the concentrations found on days four and seven, suggesting a repeated illegal drug consumption. Similiar to methadone, after application of cocaine or heroin, the main analytes excreted in all perspiration samples were cocaine and 6-acetylmorphine.

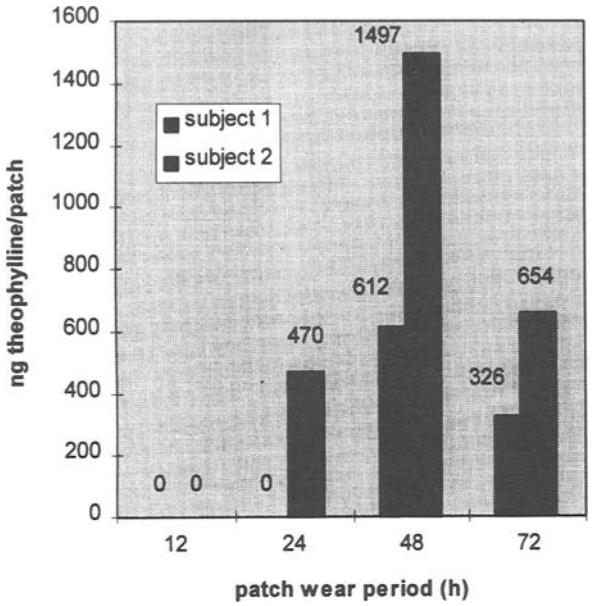

FIG. 1—*Time course of theophylline concentration (ng theophylline/patch, n = 2).*

TABLE 1—*Results of drug monitoring (GC/MS) of eight patients on chronic methadone treatment for a period of seven days of patch wear.*

Results	Patch Wear Period (Days) 2	3	4	5	7
ng Methadone/Patch					
Patient A	61	126	141	262	236
Patient B	Lp*	140	489	578	421
Patient C	146	255	208	296	86
Patient D	47	731	671	865	Ep†
Patient F	398	390	255	228	131
Patient H	858	1019	1431	Ep†	
Patient I	244	392	305	Ep†	
Patient K	142	101	373	205	294
ng EDDP/Patch					
Patient A	4	4	5	8	8
Patient B	Lp*	9	17	22	14
Patient C	7	12	6	7	4
Patient D	3	31	28	41	Ep†
Patient F	9	12	8	8	5
Patient H	26	27	57	Ep†	
Patient I	11	15	11	Ep†	
Patient K	6	4	24	17	14

*Lp = Loss of patch.
†Ep = End of patch wear period.

Discussion

The Rhodamine B experiment showed that environmental contamination is not a critical point for the application of the transcutaneous collection device tested, provided that the adhesive layer was carefully and smoothly affixed to the skin. The tightness of the polyurethane film to externally applied substances was also confirmed by Cone et al. (11) who tested the patches for passive contamination by ambient cocaine and cocaine vapors, and obtained negative results. If the patch is applied, removed, and stored properly until analysis, avoiding any external exposure to drug substances, the so-called sweat-patch testing may become a rather safe and reliable method.

The application of the patches offers the advantage of a noninvasive means compared with the analysis of blood or urine. Moreover, a surveillance period of several days seems to be possible if skin irritation due to the patch does not appear during the patch wear period.

Although it is poorly understood how nonvolatile chemicals can exit the body through the skin, there are potentially three distinct routes of penetration for small molecules from the systemic circulation to the surface of the skin: The follicular regions, the sweat ducts, the stratum corneum, or horny layer (25). Because the fractional surface of the skin appendages represents only 0.1% of the total skin surface (26), shunt diffusion through the follicles and the ducts was proposed to be of minor importance (27). In contrast,

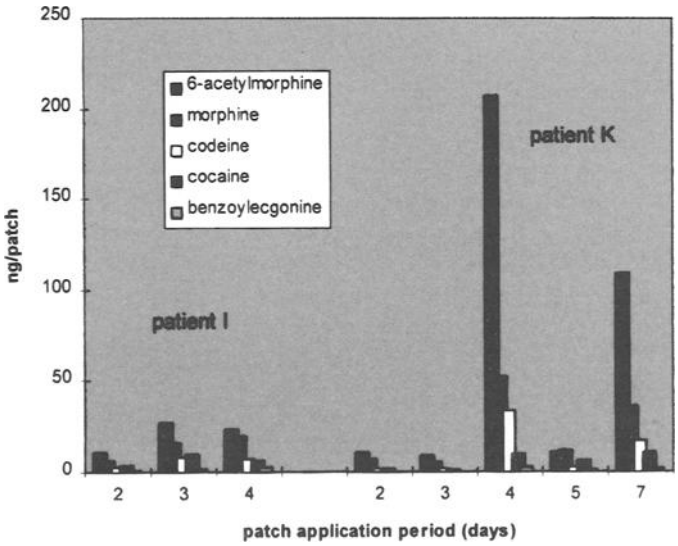

FIG. 2—*Abuse of illegal drugs by patients of a methadone treatment program. GC/MS analysis of the patches revealed the intake of heroin and cocaine during patch application period.*

there were other investigations supporting the hypothesis of an important role of the appendageal route (28). Conner et al. showed in an experiment using caffeine as a model compound that heat-provoked sweating seems to make a larger contribution to outward transcutaneous migration of the substance in the first hours. However, after 10 h, there was only a slight difference of the caffeine concentrations on a local heated area of the skin and on a nonsweating control (29). The apparent permeability coefficients of caffeine in adult volunteers and in rats were found to be similiar, although rats do not sweat. Therefore, the pathway via sweat is not available and is not likely to explain the result. The discussion and rating of the importance of the different routes of transepidermal penetration still remain controversial.

The lag time of more than 12 h as observed in the single dose experiment using theophylline may be explained by theophylline preferring passive diffusion through the stratum corneum rather than the transappendageal pathways. Because the investigation was conducted under nonthermal stress conditions, the preliminary findings indicate that the probable reason for this delay is the required period for establishing a reservoir in the horny layer. The concentrations of theophylline peaked within 24 to 48 h, as the transcutaneous collection device is a cumulative measurement tool in contrast to a plasma sample, which represents a state at a given time. The decline in theophylline concentration in the 72-h pads may be due to back diffusion into the stratum corneum and perhaps into the circulatory system as the half life (9 h) of the substance is short (30). To substantiate these first observations, these problems are currently under further investigation.

The data from the methadone study show that under steady state conditions, a period of two days seems sufficient to demonstrate a person's program compliance. The patch recorded cumulative amounts of methadone from several medications for three or four days but not for a period of seven days, because the methadone concentration did not increase consistently.

The observation that all but one of the day seven methadone and EDDP results were lower than a previous result for the patient may be caused by a regional variability of the skin to chemical permeation, or by the patch losing a constant contact with the skin surface as time passed. Peck et al. (31). concluded from a theoretical basis for the use of a transcutaneous collection device in assessing drug intake and pharmacokinetics, that the information on the cumulative amount of biologically available drug will be useful only when back transfer is minimized. This means that irreversible drug binding in the pad is a critical point. The concentrations of methadone or EDDP as measured in the pad may be further confounded by transient dispositional influences in distribution and time-dependent elimination processes.

The few data of this pilot study did not legitimate an attempt to correlate the amount of drug detected in a patch with the daily methadone dose of the patient, and they are suggested to be rather of qualitative than of quantitative nature. The questions that have arisen will be subject to further investigations.

Independent of the time of patch removal, the primary molecule was always found to be associated with a minor part of the metabolite. The less differing methadone/EDDP ratio within seven days suggests that methadone is stable on the pad for the application periods investigated. Provided that drug metabolizing in skin is not a decisive factor (32), it may be concluded from the methadone/EDDP ratio that lipid solubility is associated with the permeability of the compounds measured. This also applies for the cocaine and opiate findings. The results for cocaine are thus far in agreement with other investigators (11,12). Only 6-acetylmorphine was detected in the present study after a presumed heroin administration. Cone et al. (11) detected heroin in the patch during an interval of up to 24 h. Patches that had remained attached for a longer period showed increasing concentrations of 6-acetylmorphine and decreasing concentrations of heroin. From these data, it seems evident that heroin might be hydrolyzed during the patch wear period.

Although the new technology of transdermal drug collection requires further support and basic research, the available data already show the usefulness of the transcutaneous collection device for the surveillance of patients of a rehabilitation program and for testing of an additional abuse of illegal drugs. When the patch is correctly applied and removed by trained professionals as recommended, it may have important implications in clinical and forensic toxicology, in preventive medicine, and in prisons, as it is a relatively safe and noninvasive means offering a longer and prospective surveillance period compared with blood and urine testing.

Acknowledgment

We would like to thank Sudormed Corporation (Santa Ana, CA, USA) for the supply of the transcutaneous collection devices.

References

(1) Schottin ED. Über die chemischen Bestandtheile des Schweisses. Wunderlichs Arch physikal Heilk 1852;11:73–104.
(2) Jansch H. Zur Kenntnis gerichtlich-chemischer Untersuchungen. Beitr gerichtl Med 1922;4:55–88.
(3) Phillips M, McAlcoon MH. Sweat-patch test for alcohol consumption: evaluation in continous and episodic drinkers. Alcohol Clin Exp Res 1980;4:391–5.
(4) Phillips M. Sweat-patch test for alcohol consumption: rapid assay with an electrochemical detector. Alcohol Clin Exp Res 1982;6:532–4.
(5) Phillips M. Sweat-patch testing detects inaccurate self-reports of alcohol consumption. Alcohol Clin Exp Res 1984;8:51–3.
(6) Brown DJ. The pharmacokinetics of alcohol excretion in human perspiration. Meth Find Exp Clin Pharmacol 1985;7:539–44.
(7) Vree TB, Muskens ATJM, Van Rossum M. Excretion of amphetamines in human sweat. Int Arch Pharmacol Ther 1972;199:311–7.
(8) Suzuki SI, Inoue T, Hori H, Inayama S. Analysis of methamphetamine in hair, nail, sweat, and saliva by mass fragmentography. J Anal Toxicol 1989;13:176–8.
(9) Smith FP, Liu RH. Detection of cocaine-metabolite in perspiration stain, menstrual bloodstain, and hair. J Forensic Sci 1986; 31:1269–73.
(10) Balabanova S, Schneider E, Wepler R, Herrmann B, Boschek HJ, Schettler H. Die Bedeutung der Drogenbestimmung im Pilocarpinschweiβ für den Nachweis eines zurückliegenden Drogenkonsums. Beitr gerichtl Med 1992;50:111–5.
(11) Cone EJ, Hillsgrove MJ, Jenkins AJ, Keenan RM, Darwin, WD. Sweat testing for heroin, cocaine, and metabolites. J Anal Toxicol 1994;18:298–305.
(12) Burns M, Baselt RC. Monitoring drug use with a sweat patch: an experiment with cocaine. J Anal Toxicol 1995;19:41–8.
(13) Ishiyama I, Nagai T, Nagai T, Komuro E, Momose T, Akimori N. The significance of drug analysis of sweat in respect to rapid screening of drug abuse. Z Rechtsmed 1979;82:251–6.
(14) Henderson GL, Wilson BK. Excretion of methadone and metabolites in human sweat. Res Com Chem Pathol Pharmacol 1973;5:1–8.
(15) Balabanova S, Schneider E, Bühler G, Krause H, Das Vorhandensein von Methadon im apokrinen Schweiβ beim Menschen. Z Rechtsmed 1990;103:323–7.
(16) Cook CE, Brine DR, Jeffcoat AR, Wall JM, Wall ME, Prez-Reyes M, et al. Phencyclidine disposition after intravenous and oral doses. Clin Pharmacol Exp Ther 1982;31:625–34.

(17) Hartmann AA. Effect of occlusion on resident flora, skin-moisture and skin-pH. Arch Dermatol Res 1983;275:251–4.
(18) Aly R, Shirley C, Cunico B, Maibach HI. Effect of prolonged occlusion on the microbial flora, pH, carbon dioxide and transepidermal water loss on human skin. J Invest Dermatol 1978; 71:378–81.
(19) Haeckel R, Hänecke P. The application of saliva, sweat and tear fluid for diagnostic purposes. Ann Biol Clin 1993;50:903–10.
(20) Conner DP, Almirez RG, Rhyne P, Zameni K, Bolden BJ, Peck CC. Transcutaneous collection of theophylline: constancy and linearity of skin permeability. Skin Pharmacol 1989;2:155–61.
(21) Schneider E, Balabanova S. Nachweis von Drogen in körpernahen Wäschestücken. Arch Krim 1991;188:97–105.
(22) Tracqui A, Kintz P, Ludes B, Jamey C, Mangin P. The detection of opiate drugs in nontraditional specimen (clothing): A report of ten cases. J Forensic Sci 1995;40:263–5.
(23) Randin JP. Corrosion behaviour of nickel-containing alloys in artificial sweat. J Biomed Mater Res 1988;22:649–66.
(24) Moeller MR, Fey P, Wennig R. Simultaneous determination of drugs of abuse (opiates, cocaine and amphetamine) in human hair by GC/MS and its application to a methadone treatment program. Forensic Sci Int 1993;63:175–84.
(25) Scheuplein RJ. Transient diffusion and the relative importance of various routes of skin penetration. J Invest Dermatol 1967;84: 79–88.
(26) Pötsch L, Skopp G, Dill-Müller D, Möller MR. Theoretische Betrachtung zur Anwendung eines Perspirationspflasters—einer Möglichkeit zur prospektiven Einnahme kontrolle forensisch relevanter Substanzen. In: Althoff H, editor. Rechtsmedizin von A-Z. Kongreßbericht der 74. Jahrestagung der Deutschen Gesellschaft für Rechtsmedizin; 1995 Sept 19–23; Aachen (Germany). Aachen: Murken-Altrogge, 1995;49.
(27) Scheuplein RJ. Mechanism of percutaneous absorption I. Routes of penetration and the influence of solubility. J Invest Dermatol 1966;45:334–46.
(28) Illel B, Schaefer H, Wepierre J, Doucet O. Follicles play an important role in percutaneous absorption. J Pharm Sci 1991; 80:424–7.
(29) Conner DP, Millora E, Zamani K, Nix D, Almirez DR, Rhyne-Kirsch P, et al. Transcutaneous chemical collection of caffeine in normal subjects: Relationship to area under the plasma concentration-time curve and sweat production. J Invest Dermatol 1991;96:186–90.
(30) Moffat AC, editor. Clarke's isolation and identification of drugs in pharmaceuticals, body fluids and postmortem material. London: The Pharmaceutical Press, 1986.
(31) Peck CC, Lee K, Becker CE. Continous transepidermal drug collection: Basis for use in assessing drug intake and pharmacokinetics. J Pharmacol Biopharm 1981;9:41–58.
(32) Panatter A, Jenner B, Testa B, Jenner JC. The skin as a drug-metabolizing organ. Drug Metab Rev 1978;8:319–43.

Address requests for reprints or additional information to
Dr. Gisela Skopp
Institute of Legal Medicine
Voßstr. 2, 69115 Heidelberg
Germany