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Hair analysis interpretation in *post-mortem* situations: key considerations and proposals to overcome main hurdles

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Abstract

In the analytical challenge of *post-mortem* toxicological investigations of victim's drug history, hair analysis constitutes a useful tool. Nevertheless, in addition to usual limitations of hair result interpretation, there are additional pitfalls in *post-mortem* situations. This manuscript aims to address *post-mortem* hair analysis interpretation difficulties and proposals to overcome them. In *post-mortem* situations, mainly in cases of putrefaction, additional interpretation pitfalls are related to contamination issues consisting in drug incorporation into hair at the time of death (in case of intoxication and excessive sweating) and/or during the *post-mortem* period by putrefaction fluids. To overcome these issues, conventionally accepted criteria and considerations that must be taken into account encompass knowledge of death circumstances, confidence in analytical results, hair decontamination steps, segmental hair analysis, concentration consideration (values and hair concentration pattern), bath wash analysis results and observed parent drug/metabolites ratio. Nevertheless, none of these proposals is able to formally discriminate positive hair results related to intakes by the victim in the weeks or months before death, from hair contaminations (including those that occurred at the time of death and/or during the *post-mortem* period). A promising option could be to associate nails analysis to hair ones.

Keywords: Forensic, hair analysis, *post-mortem*, contamination

Introduction

Hair analysis that provides retrospective information on drug exposure of a victim is now well established in the forensic toxicology field. In addition, segmental analysis allows to assess the possibility of discriminating a chronic treatment from a single exposure [1]. The main routes of drug incorporation in hair are from blood (passive diffusion from blood capillaries into growing cells), sebum, sweat, and external contamination [2]. At the same time, various sources of interindividual variability, comprising genetic polymorphisms, natural hair color, metabolic disorders, diet, use of cosmetics, … can impact the drug incorporation rate in hair [3]. As a result, the final hair concentration results from a combination of different routes and means of incorporation, and there is usually no linear relationship between the drug dose absorbed and the determined hair concentration.

In addition, hair analysis interpretation is further complicated in *post-mortem* situations by body fluid contamination hazard at the time of death and/or during the *post-mortem* period. After a reminder of the main elements of hair analysis interpretation, this manuscript aims to describe these interpretation pitfalls together with means to overcome them.

Key points of hair interpretation

Generally speaking, result interpretations of drug research in hair must take into account the following points:

(1) following drug intake, drug detection in the aerial part of the hair is possible after a variable delay (but usually less than 5 days);

(2) incorporation rates of the various drugs that can be administered to the human body exhibit high variability, although basic and lipophilic substances (such as cannabis, cocaine, opioids, most psychoactive drugs, …) tend to be well incorporated [4];

(3) after intakes, drug incorporation occurs via several fluids (blood, sebum, and sweat) but also via external contamination [1];

(4) hair detection is usually coherent with repeated drug administration hypothesis, but a single intake can also be highlighted in hair using specific and sensible analytical methods [1,5];

(5) for a same substance at the same dose, hair incorporation can differ between individuals due to several factors (hair color, etc.). In addition, some cosmetic hair treatments (bleaching, dyeing, straightening, …) can not only alter drug incorporation into the hair shaft, but also their stability once incorporated. As a consequence, it is difficult to correlate the observed hair drug concentration with the drug dosage (dose unit and frequency of doses).
(6) the hair growth is assumed to be approximatively 1 cm per month (between 0.9 and 1.2 cm) in adults [6]. Accordingly, the analysis of a hair strand of x cm allows the detection of drugs (medicinal and/or toxic substances) that have been incorporated during the last x months prior to hair sampling. In this way, a segmental analysis (for instance, 4 x 2 cm-length hair segments from a hair strand of 8 cm) can be performed in order to obtain a chronological profile of drug consumption/administration: the most recent intakes corresponding to the hair segments close to the root, the older ones corresponding to hair segments close to the tip. However, the postulate of segmental analysis, based on the principle that each hair segment of a single strand corresponds to the same time period, is not necessarily true. Each strand of hair from a lock of hair can be at a variable hair growth cycle stage (anagen, catagen and telogen) and all hair strands do not necessarily have the same growth speed. In addition, hair sampling difficulties can be another source of error when establishing chronological profiles. Indeed, the hair may not be perfectly cut close to the scalp when sampling (particularly due to the position of the scissors). These issues have several interpretation consequences: (i) drugs initially present only in the proximal hair segment can be not detected if close to the hairline and the hair lock is not well sectioned; (ii) a time lag can be induced in the estimation of corresponding time drug exposure period; and more importantly, (iii) “consecutive shifts’’ can lead to “dilution effects’’ in adjacent segments [7].

In case of young children, additional elements should be taken into account:
(i) children’s hair are thinner and more porous than adult ones and hair growth speed is more variable (from 0,5 to 1,5 cm per month) [8,9].
(ii) considering new-borns, exposition during the latter months of gestation should be considered if the mother uses drugs during pregnancy, [10-12] as the fetus is exposed in the mother’s womb to certain drugs taken during pregnancy. This is especially relevant in the case of children suspected to have underwent substance abuse, as they are generally under 12 months old. This must be taken into account when performing hair analysis [9,13];

(iv) there is no existing controlled trials that provide unambiguous interpretation data for children hair concentrations. It could be argued that due to a smaller body weight, a lower dose in comparison to adults could result in hair concentration similar to adult's one.

External contaminations issues

There are some circumstances in which victim's hair analysis interpretation difficulties are enhanced, notably in *post-mortem* situations. As aforementioned, following effective drug intakes by the victim (including a chronic consumption, with repeated intakes for weeks/months before hair sampling), the endogenous incorporation into the hair is possible through several routes: blood, sebum, and sweat. But an exogenous incorporation can also occur via external contamination, where drugs get "passively" incorporated in the victim's hair [14]. As stated beforehand, segmental hair analysis supposedly allows a retracing of the chronological events regarding drug intakes. The hair concentrations observed are supposed to be an indication of the drug amounts taken beforehand. These interpretations can however be altered by situations with a high risk of external contamination, either by environment or through biological fluids:

external passive contamination due to environment of drug consumers (*e.g.* handling drugs directly or touching drug-contaminated surfaces before touching one's own hair) or even occupational exposure to pharmaceuticals should be also considered [15-17]. This route of external contamination is reported in young children, as well as in adults. It consists of a contamination involving substance residues (found in fumes, dust settling on surfaces) likely present in the living environment and that can be transfered onto hair. This phenomenon is well-described for cannabis and cocaine [11,12,18].

Hair contamination by hand of third parties should also be considered, mainly in case of young children. In fact, when the parents are drug consumers, drug particles can easily be found on parents' fingers and therefore be dropped off on the child's hair after caresses, hairdressing… Studies (involving amphetamine derivatives, *e.g.*, MDMA) achieved in our laboratory allow us to think that, in some particular cases, this type of transfer can lead to positive results despite preliminary steps of hair decontamination before analysis. In the literature, this phenomenon has already been described for numerous substances, especially for cannabis, cocaine, methadone… [11,16,19].

Hair contamination by sweat of third parties also mainly concern children. The scientific literature reports mothers under methadone embracing their child or sharing their bed with him/her, leading to direct or indirect (bedding) contamination of the child's hair by the mother's sweat [20]. Many drugs (and their metabolites) can indeed be found in sweat of consuming parents and then found in their child's hair, whether from a direct or indirect contact (clothing, household linen, …) or simply through hand contact [10,11,21].

As a consequence and in these situations, (i) the impact of external contamination is usually objectified by increasing concentrations along hair strands, with concentrations being higher the closer we get to the hair tips (due to the time accumulation of drugs in the older hair segments) [19], and (ii) owing to this additional difficulty, drug hair detection as the only result is insufficient to properly characterise a repeated exposition in young children.

Additional interpretation pitfalls in *post-mortem* situations

In *post-mortem* situations, especially in cases of significant putrefaction, the paramount problem consists in external contamination, *i.e.,* a risk of misinterpretation of hair results due to drug incorporation into the hairy element at the time of death and/or after the corpse decomposition during the *post-mortem* period [23-26].

At the time of death, hair contamination by the victim's one sweat may occur in some circumstances related to (i) case of death from acute poisoning in which the drug (and metabolites) will naturally be found in the victim's sweat in high quantity, and (ii) exaggerated sweating due to the poisoning. In these specific situations, sweat will impregnate the victim's hair, and the drug (and metabolites) may be found along the entire hair strand (and not only in the proximal capillary segment). This is a known occurrence in intensive care with fentanyl (used as an anesthetic drug in a hospital setting), when hair is sampled from admitted victims. The (usually unconscious) patient is lying on a hospital bed for intensive care, which (for hygiene purposes) has a synthetic linen (favoring perspiration): hair sampled from patients in those conditions is therefore regularly soaked with sweat. A positive hair result regarding fentanyl (which is generally administered to the victim) must therefore be interpreted cautiously as it is clearly established that it can be the result of a recent contamination through sweat. Fentanyl can indeed diffuse extensively into hair [27], contaminate the entirety of hair strands, and, thus, be found in sampled hair despite pre-analytical decontamination steps [28]. In *post-mortem* situations, this kind of contamination is

observed in fatal poisoning cases associated with an excessive perspiration. This is notably the case in malignant hyperthermia episodes caused by amphetamine derivatives (*e.g.,* in case of hyperthermia due to fatal intoxication related to amphetamine derivatives) or in serotoninergic syndrome situations [22,23,29-30].

External hair contamination by body fluids also arises in the case of hair sampled from decaying corpses. In this particular situation, hair result interpretation must take into account that hair may have soaked in putrefaction fluids and that the whole hair strands can be therefore contaminated by drugs present in those fluids after prolonged contact [22-26].

Means to overcome these difficulties

The aforementioned situations can be considered as external contamination (or exogenous incorporation), which can interfere with the segmental hair analysis interpretation (x cm corresponding to x months) and, thus, prevent from a correct appreciation of drug intake history of the victim, as well as of drug doses consumed during the weeks and months preceding the time of death. Accordingly, following steps and conventionally accepted criteria must be taken into account [24,32]:

(1) First and foremost, taking commemorative events and medical history (the victim's story, the clinical signs, the circumstances of death…) into account, as well as the sampling context, is a crucial step to inform and alert the forensic expert on possible external contaminations [12].

(2) In the same way, it is necessary to have confidence in the analytical results. Trusting results arise from proper pre-analytical (hair pre-treatment, segmentation) and analytical methods that will minimize the risk of false positive results. The assurance of result quality relies on the use of appropriate tools (generally chromatography coupled with tandem mass spectrometry) and the application of stringent detection/identification criteria (retention time and at least 2 mass transitions per substance) [1,12,14,33].

(3) Regarding pre-analytical steps, a systematic washing is applied to hair samples in order to remove external pollutants. The necessity of this washing step in every circumstances is consensual and applied by most, if not all, laboratories involved in forensic hair analysis. [1,15,25,33,34]. International recommendations promote washing with both aqueous and organic solvents, but also additional washing baths when the hair is heavily soiled with corporal fluids. On the other hand, it is clear that there is no consensus, nor uniformity

between the different laboratories regarding these decontamination procedures. Various agents are used in hair washing baths, such as shampoos, surgical disinfection solutions, surfactants like dodecylsulfate, phosphate buffers, or even organic solvents like acetone, diethyl ether, methanol, ethanol, dichloromethane, hexane or pentane… at various concentrations and contact times. Generally, but not systematically, this hair decontamination step consists in procedures similar to the one implemented in our laboratory: 2 baths of 5 minutes in lukewarm water, followed by 2 baths of 5 minutes in dichloromethane. It must be noted that this washing procedure not only removes the substances present at the surface of the hair, but can also remove endogenously- or exogenously-incorporated substances. Many authors have done testing in order to define and evaluate what would be an "ideal" washing procedure that would only remove from the hair substances externally incorporated due to contamination [14,32,34-37]. Their conclusion is that it is not possible to eliminate substances originating from external contamination without impacting substances present in the hair due to internal exposure, even by using the most sophisticated washing procedure [16,22,35]. To summarize, decontamination procedures (e.g. two water baths followed by two dichloromethane ones) are not able to neither completely remove external contamination in case of *post-mortem* specimens, nor to differentiate without any doubt artefact(s) from *antemortem* drug use [14,32,34,35,38].

(4) Hair concentration levels should be considered. Taking into account the positivity cut-offs (when available) to interpret the results is a prerequisite. For most substances, in particular narcotics, learned societies such as the Society of Hair Testing (SoHT) recommend the use of cut-offs, *i.e.* concentration thresholds below which the results should be considered negative [33]. However, those cut-offs are only a prerequisite to consider a result positive. They not only exist to overcome contamination problems, but also physiological considerations regarding hair growth rates and cycles, etc. It is clear that a result higher than those cut-offs cannot exclude important contamination as previously described [14]. Comparison between the observed hair concentrations and the highest published ones is unavoidable when facing very high concentrations in the victim's hair sample. For instance, contamination by body fluids and decomposed tissues during the putrefaction process remains the best explanation when observed hair concentrations are significantly higher (2 times or more) than the highest published concentrations reported for regular/intensive users or abusers [24]. With a massive external contamination (by biological fluids and most notably putrefaction fluids), concentrations found can be far too elevated to conform to a single exposure, even if it was a quantitatively important and extensive exposure [24,25].

(5) Searching for metabolites in hair is another useful criterion to appreciate the likelihood of facing an external contamination. The presence of one or several metabolites of the parent drug is indeed usually the sign of its endogenous metabolism by the victim's organism. This research is consistently done, although metabolites tend to be less easily hair incorporated than parent substances [1,39]. It is also interesting to determine the metabolite(s)/parent drug concentration ratios to assess a possible external contamination: as seen previously, this is systematically the case with cocaine [33,40] and can be applied for some pharmaceuticals [17]. However, although the presence of metabolites in hair dismisses a possible environmental contamination through contact, it does not exclude situations involving contamination by sweat or other biological fluids (*e.g.* in the hypothesis of hair soaking in putrefaction fluids during the *post-mortem* period or of sweat containing metabolites at the time of death) [22,38].

(6) Performing bash wash analysis in order to assess external *post-mortem* contamination is a consensual and systematic practice in most laboratories, based on the idea that if the external contamination is significant, the washing baths will be enriched with the corresponding substances. This assessment is in sort a little like analyzing bath water to appreciate the degree of dirtiness from whom took the bath. As such, the latest or both latest dichloromethane baths from the decontamination step are classically analyzed alongside samples to assess the presence of substances and their respective concentration. This approach has been the subject of several studies [32,35]. Generally, when substances are detected in hair but are not present in the washing baths, potential external contamination can be rejected. On the contrary, when concentrations in the washing baths are higher than the ones in hair, authors conclude to a probable presence in hair due to external contamination [22,23,25,32]. The question of situation "in between" arises when concentrations in hair and wash baths are of similar magnitude. In our practice, the second dichloromethane washing bath solution is analysed and the results obtained in the wash residue are compared to those observed in the hair samples: when the ratio wash bath/hair is higher than 0.1, the possibility of external contamination is considered, although it cannot be asserted [14,22-24,32].

(7) Segmental hair analysis should be promoted in *post-mortem* situations. Indeed, the presence of homogeneous concentrations in segmental hair analysis, meaning similar concentrations in the different hair segments alongside the hair lock, is in favor of an external contamination at the time of death. This segmental analysis is strongly recommended by international consensus, particularly to help to differentiate endogenous from exogenous incorporation [33]. This criterion is based on the principle that if hair were subjected to an

external contamination by biological fluids, it would impact the entirety of the hair in a similar way and would consequently give rise to identical concentrations in all hair segments [22-24]. Nevertheless, even if it is obvious that homogeneous concentrations along the hair shaft after segmental analysis could be indicative of external contamination (via contamination from sweat produced close to the death or via body fluids during the *post-mortem* period) [41], it is not always possible to perform segmental analysis in cases of putrefied bodies due to particular circumstances (sampling a hair strand with location of root-tip is typically not possible when only some hair strands attached to the skull and mixed with decomposed tissues are available) or when the hair are too short (< 3 cm) [23].

(8) Finally, it is obvious that the interpretation of *post-mortem* hair analysis results should also take into account the toxicological results obtained in the other *post-mortem* biological samples of the victim. In this context, although the use of nails as a complementary matrix to establish proof of exposure is still currently unusual (and as reported nail drug concentrations remain limited), nail analysis can provide complementary information to hair ones [25,42]. Taking into account the nail growth speed (approximatively 3 and 1.1 mm per month for fingernails and toenails, respectively) together with drug incorporation along the whole length of nails, the detection window of drugs in nail clipping samples (it is of note that segmental analyses cannot be performed in nails) is estimated to be from 3 to 6 and 8 to 16 months in fingernails and toenails, respectively [43-45]. Drug concentrations are usually higher in fingernails than in toenails, and concentrations in nails are correlated to the hair's ones. However, hair/nail concentration ratios (parent drug or metabolite ratio) seem to be variable depending on substances [42,46,47]. As for hair, the main problem of *post-mortem* nail analysis interpretation consists in the external contamination issue. Nevertheless, it has been suggested that this phenomenon could be negligible in nails, especially in toenails [47,48] which are generally protected from environmental exposure. Consequently, in addition to hair results, and taking into account drug detection windows (which are fixed in contrast with hair ones which are dependant on hair length), as well as differences in metabolic ratio and reduced contamination issues, nails analysis has been reported to be contributory in forensic investigations in several cases and tricky situations. This was recently illustrated (i) by the case of a 5-week-old infant victim of an acute intoxication with bromazepam, where the possibility of repeated bromazepam exposure since birth was examined by combined analysis of hair and nails [49], and (ii) in a criminal case where the perpetrator could have been under the influence of 25I-NBOMe and 4-MMC at the time of the incident, and for which the combination of head hair, axillary hair, and toenail clipping toxicological analysis results

allowed to exclude external contamination during the time the subject was in prison and to narrow the estimation of the drug use period (finally consistent with consumption of both drugs at the time of the crime) [50]. In *post-mortem* situations, the complementary of nail and hair analyses was demonstrated in a fatality of a 32-month-old child for whom a 3-cm segmental hair analysis of a 6-cm hair lock revealed the presence of methadone in both the proximal and distal segments: methadone detection in nail samples confirmed repeated methadone administration over time [51]. In another case, finger nail (obtained by clipping after body exhumation) analyses were negative for cyamemazine whereas cyamemazine was detected in hair (also collected after exhumation), allowing to conclude (i) that the subject was likely naive for this drug and died from an acute cyamemazine overdose in a suicidal context, and (ii) that observed positive results in hair were possibly due to prolonged contact with the putrefactive organic material [23]. Lastly, in a sudden unexpected infant death case related to tramadol intoxication, the combination of results (and metabolite ratio calculation) observed in both head hair and nail samples (from the victim and his mother, father, and young sister) allowed the authors to dismiss the hypothesis of repeated tramadol administrations to the infant before the fatal accidental intoxication [52].

Conclusion

Finally, the most serious pitfalls of hair analysis do not remain in the assay performance but in the result interpretation [1,14,32]. Anyway, a positive result in a hair sample collected *post-mortem* indicates that the victim consumed the compound at any time, several days or weeks before the decease and/or at the time of death. It remains obvious that, currently, none of the above proposed criteria or steps is infallible to formally discriminate drug presence in hair related to *antemortem* intakes by the victim in the weeks or months before death from hair contaminations (including those that occurred in *perimortem* or *post-mortem* periods) [14,16]. Nevertheless, in this analytical challenge of *post-mortem* toxicological investigations of a victim's drug history, a promising option could be to combine nail and hair analyses. Indeed, even if the use of nails in forensic toxicology is still rare and the interpretation of observed concentration in nails remains limited, nail analysis can provide useful complementary information to hair ones [23,51,52].

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