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Contribution of in utero drug exposure when interpreting hair results in young children☆

P. Kintz [a,b,*]

[a] X-Pertise Consulting, 84 route de Saverne, F-67205 Oberhausbergen, France
[b] Institut de Médecine légale, 11 rue Humann, F-67000 Strasbourg, France

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ABSTRACT

Hair specimen is necessary to complement blood and/or urine analyses as it permits differentiation of a single exposure from chronic use of a drug by segmentation of the hair for a stated growth period. Moreover, due to a frequent long delay between event and police declaration, hair can be the only solution for lack of corroborative evidence of a committed crime. With the exception of lower amount of biological material in children versus adults, there is no specific analytical problem when processing samples from children. The issue is the interpretation of the findings, with respect to the different pharmacological parameters. In some very young children, the interpretation can be complicated by potential in utero exposure.

Twenty-four cases from daily practice have been reviewed. Children were less than 1 year old, hair was always longer than 4 cm and the corresponding mothers admitted having used drugs during pregnancy.

Drugs involved include methadone, tramadol, diphenhydramine, diazepam, cannabis, heroin, amitriptyline and bromazepam. Analyses were achieved by hyphenated chromatographic validated procedures after hair decontamination and segmentation.

The concentrations measured in the hair of children were lower than those observed in subjects using therapeutically (or illegally) these drugs. In that sense, the frequency of exposures appears as unfrequent (low level of exposure), with marked decrease in the more recent period. However, the parents denied any administration in all cases and there was no reason to suspect re-exposure after delivery and no clinical problem during the period between delivery and hair collection during regular visits to the physician was noticed. The pattern of drug distribution was similar in all these cases, low concentrations in the proximal segments and highest concentration in the distal segment (last segment). When considering the concentration in the distal segment as the 100% of the response (highest concentration), after analysis of 4 segments (irrespective of the length of the segment but longer than 1 cm), it was observed the following pattern: proximal segment, 5–35% of the response; segment 2, 15–50% of the response; segment 3, 25–60% of the response; and distal segment, 100% of the response.

It is proposed to consider 100% in utero contribution to the final interpretation when the ratio concentration of the proximal segment to the concentration of the distal segment is lower than 0.5. This can be applied only when the child is under 1 year old and the hair shaft length is at least 4 cm (to achieve suitable segmentation). It is important, when using this cut-off to have at least 3 or 4 segments to be able to observe the variation in drug concentrations, whatever the length of each segment (>1 cm).

1. Introduction

Whereas the detection of drugs in a child's hair unambiguously shows drug handling in the environment of the child, it is difficult to distinguish between systemic incorporation into hair after ingestion or inhalation and external deposition into hair from smoke, dust, or contaminated surfaces. However, the interpretation of hair results with respect to systemic or only external

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* Correspondence to: X-Pertise Consulting, 84 route de Saverne, F-67205 Oberhausbergen, France. Tel.: +33 388266431; fax: +33 388272403.
E-mail addresses: pascal.kintz@wanadoo.fr, pkintz@x-pertise.com

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exposure is particularly important in case of children for a realistic assessment of the toxic health risk.

Excepting the lower amount of biological material in children versus adults, there is no specific analytical problem when processing samples from children. Obviously, the same procedure can be used. The issue is the interpretation of the findings, with respect to the different pharmacological parameters.

There are many differences between the hair from children and those from adults: the hair from children is thinner and more porous, the ratio of anagen/catagen phases is not maintained, and the growth rate can be different, at some periods, from the usual 1 cm/month [1].

In adults, hair shaft begins in cells located in a germination centre, called the matrix, located in the base of the follicle. Hair does not grow continually, but in cycles, alternating between periods of growth and quiescence. A follicle that is actively producing hair is said to be in the anagen phase. Hair is produced during 4–8 years for head hair (<6 months for non-head hair) at a rate of approximately 0.22–0.52 mm/day or 0.6–1.42 cm/month [2] for head hair (growth rate depending of hair type and anatomical location). After this period, the follicle enters a relatively short transition period of about 2 weeks, known as the catagen phase, during which cell division stops and the follicle begins to degenerate. Following the transition phase, the hair follicle enters a resting or quiescent period, known as the telogen phase (10 weeks), in which the hair shaft stops growing completely and the hair begins to shut down. Factors such as race, disease states, nutritional deficiencies and age are known to influence both the rate of growth and the length of the quiescent period. On the scalp of an adult, approximately 85% of the hair is in the growing phase and the remaining 15% is in a resting stage [2].

An extensive literature search, in libraries (University of Strasbourg, medicine and science), database, Google and on PubMed, performed on 10 July 2014 with the following key words "hair, anatomy, neonate, new-born, growth, physiology" was unable to produce recent citation about the anatomy of hair in new-borns and very young children. It was necessary to go back to 1927 [3] to identify the following anatomical features. In utero, the activation of the hair follicles of the foetus starts at about the 4th month of pregnancy to produce the lanugo, which is very thin, curly and non-pigmented. The lanugo will be replaced by a down, short, non-pigmented, thin (between 5 and 40 μm), with a slow growing rate and located between 0.5 and 1.5 mm under the skin. Starting the 8th month of pregnancy, the final hair will appear. It is long, pigmented, thick (more than 80 μm), with a rapid growing rate, and located between 2.5 and 5 mm under the skin. After delivery, to avoid becoming bald, hair growing is asynchronous (variation in the anagen/catagen phases) during the first 3–4 months. One will observe hair loss during the first 6 months after delivery, followed by a slow growing rate during the next 6 months. After 1 year, the normal rate of hair growth (1 cm/month such as in adults) starts. The growth rate is first 0.2 mm/day, and then it increases to 0.3–0.5 mm/day, to finally be stabilized at about 0.35 mm/day.

As a consequence, it is very difficult to put any window of detection when testing for drugs in young children. It is even more complicated as it has been demonstrated that drugs can be incorporated during pregnancy in the hair of the foetus, which will contribute to the positive findings after delivery [4–7]. Identification of a drug in hair after delivery can indicate: 1, in utero exposure, or 2, exposure after delivery, or 3, a mix of both situations. No paper has been published about the disappearance of drug after discontinuation of use or exposure (in case of in utero exposure). In adults, it can take 3–6 months to have a negative hair result after heroin or cocaine abstinence [8,9]. Other drugs have not yet been studied. The time course after delivery of disappearance of a drug incorporated during pregnancy has never been reported.

The present paper deals with the interpretation of 24 cases where children were exposed to drug(s) during pregnancy and evaluation of in utero contribution to the final measured concentrations.

2. Materials and methods

Between March 2010 and March 2014, 24 cases were received. The request was to verify if there was any evidence of historical drug exposure by the donor of the sample. The items were received sealed and the chain of custody was intact. The samples were logged onto the system and processed at the laboratory. These samples were both clinical (admission to the hospital for unspecific diseases) and forensic (child custody, divorce, sudden child death) from children aged less than 1 year. Medical staff or social workers wanted to verify potential drug administration or passive exposure to drugs after delivery. All the parents denied any administration to the child after delivery, but all the mothers admitted drug use during pregnancy. No drug was administered to the children to treat withdrawal symptoms after delivery. The physicians in charge of the children never noticed a clinical problem during the period between delivery and hair collection. Parents' hair was not tested. It can be considered that claims of abstinence based on self-report can be a limitation of the findings.

The hair samples were at least 4 cm in length and tested by segmentation (4 segments) after decontamination for pharmaceuticals by LC–MS/MS using validated analytical procedures [10–13]. Drugs of abuse were first screened by ELISA, and then confirmed by GC/MS [14].

3. Results and discussion

The following case is an example of the difficulties to interpret the hair finding in young children. The subject is an 11-month-old girl often found sedated. The mother was using methadone during pregnancy and was, at the time of hair collection, under methadone therapy. The results of the hair analysis of the child are presented in Table 1. Methadone tested positive in all 4 segments, with lower concentrations in the more recent period. A least, four possible interpretations of the measured drug concentrations can be addressed: (1) decrease in administration in the more recent period; (2) increase of body weight due to growing, so the same dosage will result in lower concentrations in hair; (3) sweat contamination from the parents/mother at the time the child is with them in bed, the older hair being longer in contact with the bedding; and (4) contribution (from 0 to 100%) of in utero exposure during pregnancy. There appears to be no distinguishing between drug incorporated from the mother in utero via blood, and the potential for drug incorporation in new born hair from having constant contact with amniotic fluid which has been shown to contain drugs. However, both account for in utero exposure.

In this case, points 1 and 2 can be excluded, given there was no obvious reasons to suggest exposure of the child after delivery (suggested by the physician in charge of the child). About point 3, a

Table 1
Methadone distribution in the hair of an 11-month-old girl.

Segment (cm)	Methadone (ng/mg)	EDDP (ng/mg)
0–1.5	0.32	<0.01
1.5–3	0.46	<0.01
3–4.5	0.59	0.09
4.5–6	1.58	0.20