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Tin hair analysis in poly symptomatic patients with Essure® implant

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Abstract

Objective: Essure® is a permanently implanted contraceptive device withdrawn from the market in 2018 because of adverse effects associated with this device, including gynecological disorders and extrapelvic symptoms. After surgical removal device, examination of uterine biopsies showed the frequent presence of tin resulting from implant degradation. In this context, the biological monitoring of tin metal in implanted patients becomes an issue of capital importance since hair is the best matrix to reveal long-term metallic exposure.

Methods: The aim of this retrospective study was to compare hair chromium, nickel and tin levels in 10 Essure® implanted patients (aged 50±2 years old) presenting with adverse events, in particular psychosomatic manifestations, with 25 healthy non implanted volunteers' group (aged 47± 4 years old). Hair chromium, nickel and tin analyses were performed on a 7800 ICP-MS inductively coupled plasma mass spectrometer.

Results: For the group of healthy subjects, all tin concentrations in hair (25/25) were below the quantification limit of 0.1 µg/g, with 2 concentrations above the detection limit of 0.07 µg/g. Similarly, all nickel and chromium concentrations (25/25) were below the quantification limit, with 2 Cr concentrations and one Ni concentration above the detection limit of 0.1 µg/g.

In the implanted group, subjects had mean hair concentrations of nickel and tin of 0.94+0.39 µg/g and 0.25 ± 0.17 µg/g respectively. All subjects (10/10) had chromium concentrations below the limit of quantification.

For nickel and tin assays in hair above the quantification thresholds, there were positive correlations between (a) nickel or tin concentrations and the duration of device implantation (correlation coefficient of 0.79 for tin and 0.44 for nickel) and between (b) tin concentration and the multiplicity of extra-pelvic symptoms (correlation coefficient of 0.76), with (c) no correlation observed between nickel concentration and symptom multiplicity.

Conclusion: Tin seems to be an important factor involved in the physio pathogenesis of extra pelvic symptoms in patients with the Essure® medical device. In this context, the hair tin analysis is a useful tool in the monitoring of patients with Essure® implants.

Keywords: Essure; Hair analysis; Tin; Contraceptive device; Pharmacovigilance

1. Introduction

Essure® (Bayer AG, Leverkusen, Germany) is a permanently implanted birth control device for women marketed since 2002 [1]. It is made up of a complex composition of metallic elements including 4 metallic alloys: 316 L stainless steel

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[stainless steel, iron (Fe), 16-18% by weight of chromium (Cr), 10-14% by weight of nickel (Ni), 2-3 wt% molybdenum (Mo)], nickel-titanium [Ni-Ti, 55 wt% Ni and 45 wt% titanium (Ti)], tin-silver [(Sn-Ag, 95% wt Tin (Sn) and 5% wt Silver (Ag)] and Platinum-Iridium [(Pt-Ir, 90% wt Platinum (Pt) and 10% wt Iridium (Ir)] [2]. its marketing was stopped in 2018 because of adverse effects associated with this device, including gynecological disorders (pain, menorrhagia), but also broad extrapelvic symptoms (persistent asthenia and fatigue, heart palpitations, tinnitus, pruritus, joint and / or muscularis pain, skin rashes, digestive disorders)[3]. After surgical removal device, anatomopathological examination of uterine biopsies using scanning electron microscopy coupled with energy dispersive X-ray (SEM-EDX) showed more frequently the presence of tin [4]. These particles could be responsible for granulomatous inflammations as well as local symptoms and many of the systemic symptoms would be consistent with probable chronic organotin poisoning. In this context, the biological monitoring of tin metal in implanted patients becomes an issue of capital importance. However, except the mineral analysis from the excisional biopsy, there are currently no validated analytical criteria for monitoring the tin release and its impregnation for these patients [4]. Unfortunately, analysis of the blood does not reflect the actual metallic concentration in the whole body because the organism provides homeostatic mechanisms that mask disturbances in the administration of metals. In these conditions, hair analysis of metallic elements is crucial because hair is the best matrix to reveal long-term exposure to inorganic pollutants [5].

The aim of the study was to compare hair chromium, nickel and tin levels in Essure® implanted patients presenting with adverse events, in particular psychosomatic manifestations, with healthy non implanted volunteers' group.

2. Material and methods

In this retrospective study were included 25 healthy subjects (aged 47±4 years old) without any contraceptive device and 10 subjects aged 50±2 years old suffered from extra-gynecological symptoms (such as persistent asthenia, heart palpitations, insomnia, tinnitus, digestive disorders, etc.…) since their Essure® procedure.

All included subjects provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

The hair was collected in specific conical tubes of about 3 cm representing an average of 3 months of exposure. The samples are taken in duplicate and placed in different tubes, the first tube is used for LC-MS-QTOF analysis for organic pollutants screening and the second tube for ICP-MS analysis for metal screening [6].

These analyses were performed on a 7800 ICP-MS inductively coupled plasma mass spectrometer (Agilent, France).

The calibration curves extend from 0.001 µg/L to 25 µg/L and is performed with a dilution solution comprising 0.2% Trace Metal nitric acid (Fischer, UK), 0.1% Triton X100 (Agilent, France) in ultrapure water (quality grade >18,2 Mega Ohm). To build these calibration curve, we use solution standard solutions No. IV-ICPMS-71A, No. IV-ICPMS-71B, No. MSHG-10PPM (Inorganic Venture, Canada). An exact amount of hair (20 to 40 mg) is mineralized in 69% Trace Metal Grade nitric acid (Fischer, UK). The solution obtained is diluted to 100th with solution standard solutions No. IV-ICPMS-71A, No. IV-ICPMS-71B, No. MSHG-10PPM (Inorganic Venture, Canada). Chromium, nickel and tin concentrations were quantified using external standards. The data is reprocessed with Agilent's ICP Masshunter™ Data Analysis software.

The statistical analyses were carried out by Microsoft Excel 2021™.

3. Results

Ten women (aged 50±2 years old) with Essure® device and 25 healthy subjects (aged 47±4 years old) were included All implanted women have at least 3 of the following persistent extra-gynecological symptoms (Table 1): Fatigue Insomnia, Headaches, Paresthesia, Heart palpitation and Thoracic oppression, Vertigo, Tinnitus, Poor concentration and lack of focus, Digestive disorders, Appetite disorder.

For the group of healthy subjects (Table 2), all tin concentrations in hair (25/25) were below the quantification threshold of 0.1 µg/g, including 2 concentrations above the detection threshold of 0.07 µg/g. Similarly, all nickel and chromium concentrations (25/25) were below the quantification limit, with 2 chromium and one nickel concentrations above the detection limit. Subject number 10 showed a concomitant presence of chromium and nickel, but no tin.

Table 1 Reported symptoms

Reported symptoms	Number of patients (proportion)
Fatigue	10 (10/10)
Insomnia	10 (10/10)
Headaches	7 (7/10)
Paresthesia	2 (2/10)
Heart palpitation and Thoracic oppression	2 (2/10)
Vertigo / Tinnitus	4 (4/10)
Poor concentration and lack of focus	10 (10/10)
Digestive disorders	3 (3/10)
Appetite disorder	2 (2/10)

Table 2 Epidemiological, clinical, and analytical characteristics of the control group

Subject Number #	Age (year)	Chromium concentration (µg/g)	Nickel concentration (µg/g)	Tin concentration (µg/g)
#1	43	-	-	-
#2	50	-	-	Present (0.07<[Sn] <0.1)
#3	47	-	-	
#4	50	-	-	-
#5	50	-	-	-
#6	51	-	-	-
#7	39	-	-	-
#8	51	-	-	-
#9	48	-	-	-
#10	47	Present (0.1<[Cr] <1.0)	Present (0.1<[Ni] <1.0)	-
#11	40	-		-
#12	44	-	-	-
#13	49	-	-	-
#14	43	-	-	-
#15	38	-	-	-
#16	52	Present (0.1<[Cr] <1.0)	-	-
#17	47	-	-	-
#18	49	-	-	-
#19	42	-	-	-
#20	48	-	-	-
#21	52	-	-	-
#22	50	-	-	-

#23	52	-	-	-
#24	49	-	-	Present (0.07<[Sn] <0.1)
#25	51	-	-	
N=25	47.3±4.2	Presence of Cr (2/25) (0.1<[Cr] <1.0)	Presence of Ni (1/25) (0.1<[Ni] <1.0)	Presence of Sn (2/25) (0.07<[Sn] <0.1)
Mean		Absence of Cr (23/25) 0.072 µg/g	Absence of Ni (24/25) 0.035 µg/g	Absence of Sn (23/25) 0,007 µg/g
(Max, min)		(0.9, 0.0 µg/g)	(0.9, 0.0 µg/g)	(0.09, 0.0 µg/g)

Table 3 Epidemiological, clinical, and analytical characteristics of the patients

Subject	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**	**#7**	**#8**	**#9**	**#10**
Age	51	48	50	52	47	53	48	49	52	50
Implantation duration (years)	6	10	8	10	5	13	9	6	5	7
Fatigue	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present
Insomnia	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present
Headaches	Present	Present	/	Present	/	/	Present	Present	Present	Present
Paresthesia	/	/	Present	Present	/	/	/	/	/	/
Heart Palpitations	/	/	Present	Present	/	/	/	/	/	/
Vertigo Tinnitus	Present	Present	Present	/	/	/	/	/	/	Present
Poor concentration lack of focus	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present
Digestive disorders	/	/	Present	Present	/	Present	/	/	/	/
Appetite disorder	/	/	Present	Present	/	/	/	/	/	/
Symptoms Number	5	5	8	8	3	4	4	4	4	5
Tin concentration (µg/g)	0.19	0.3	LOD<[Sn] <LOQ (0.07<[Sn]<0.1)	0.8	0.15	LOD<[Sn] <LOQ 0.07<[Sn] <0.1	0.55	0.12	0.18	0.25
Chromium concentration (µg/g)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr] <LOQ (0.1<[Cr] <1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr] <LOQ (0.1<[Cr] <1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)	LOD<[Cr]<LOQ (0.1<[Cr]<1)
Nickel concentration (µg/g)	LOD<[Ni]<LOQ (0.1<[Ni]<1)	1.0	LOD<[Ni] <LOQ (0.1<[Ni] <1)	1.2	1.1	1.7	1.6	LOD<[Ni]<LOQ (0.1<[Ni]<1)	LOD<[Ni]<LOQ (0.1<[Ni]<1)	LOD<[Ni]<LOQ (0.1<[Ni]<1)

With: LOD: limit of quantification, LOD: limit of detection

Table 4 Correlation coefficient values

	Implant duration	Symptoms number	Tin concentration	Nickel	Chromium
Implant duration	-	0.79	0.79	0.54	NA
Symptoms Number	0.79	-	0.76	-0.24	NA
Tin concentration	0.79	0.76	-	0.44	NA
Nickel	0.54	-0.24	0.44	-	NA
Chromium*	NA	NA	NA	NA	NA

NA: not applicable since all chromium concentrations (25/25) were below the quantification threshold

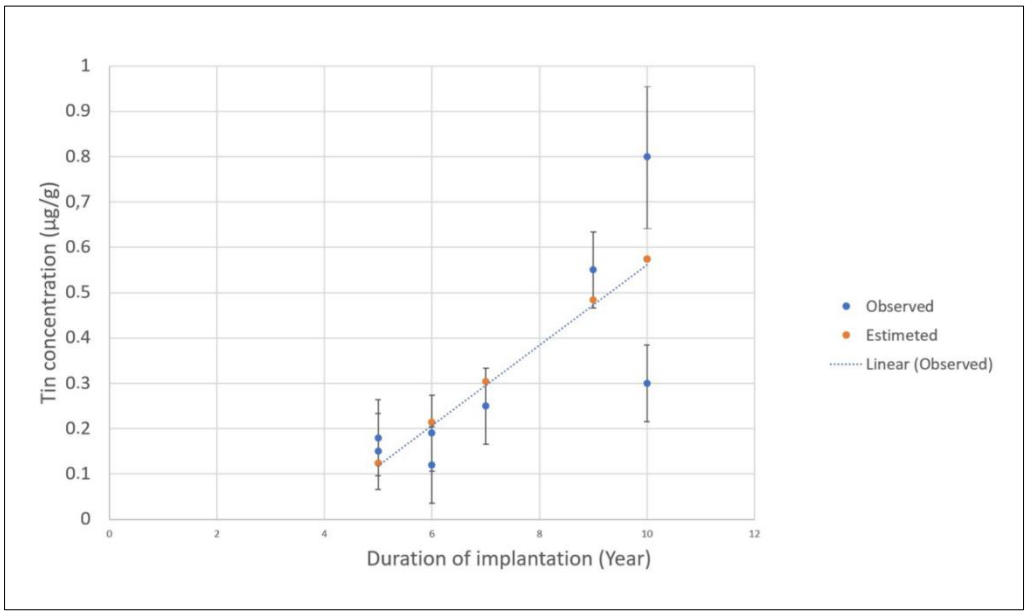

Figure 1 Modelling curve of the tin concentration as a function of the implantation time

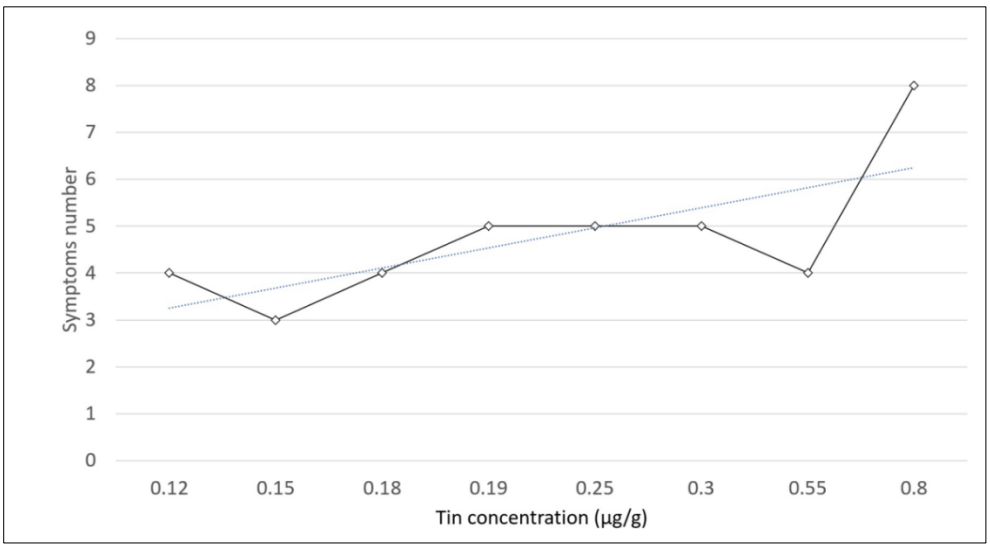

Figure 2 Modelling curve of symptoms number as a function of the tin concentration

In the implanted group, the subjects had a mean hair nickel and tin concentrations of 0.94+0.39 µg/g and 0.25 ± 0.17 µg/g respectively. Mean nickel and tin concentrations in the implanted group versus the control group were significantly higher: for nickel 0.94+0.39 µg/g versus 0.07+0.05µg/g and for tin 0.25 ± 0.17 µg/g versus 0.007±0.005 µg/g, p<0.003).

All subjects (10/10) had chromium, nickel and tin concentrations above detection limits (LOD_{Cr}: 0.1µg/g, LOD_{Ni}: 0.1µg/g and LOD_{Sn}: 0.07µg/g):

- For chromium, 10/10 were below the limit of quantification (<1µg/g).
- For nickel, 5 (5/10) were above the limit of quantification (LOQ >1µg/g) and 5 between the two limits LD and LQ (0.1µg/g< nickel concentration in hair <1µg/g).
- For tin, 8 (8/10) were above the quantification threshold (LOQ >0.1µg/g) and 2 (2/10) between the two limits LOD and LOQ (0.07µg/g<tin concentration in hair <0.1µg/g).

Table 4 describes the relationships between implant duration, symptom multiplicity, and chromium and tin concentrations above the quantification threshold (tin n=8, nickel n=5):

- there is a positive correlation (0.79 for tin and 0.44 for nickel) between tin and nickel concentration and the duration of device implantation.
- there is a positive correlation (0.79 for tin and 0.54 for nickel) between the multiplicity of symptoms and the duration of device implantation.
- there is a positive correlation of 0.76 between hair tin concentration and multiple symptoms, and no correlation between hair nickel concentration and multiplicity of symptoms.
- Finally, there is a correlation of 0.44 (weak correlation) between tin and nickel concentrations in the hair.

4. Discussion

Essure® is an expandable spring device (2 mm diameter, 4 cm long) of metallic complex of stainless steel, chromium, platinum, iridium, and tin-silver containing Dacron fibers that induce an inflammatory response and final fibrosis of the intramural tubal lumen [7-8].

It was marketed in France between 2002 and 2013 by Conceptus, then by Bayer Pharma AG until August 2017. Following reports of adverse events during placement and after implant placement, the health authorities have implemented enhanced surveillance of this device in France. Since August 2017, the implant is no longer used in France and since the end of 2018, it is no longer marketed in any country. Indeed, many patients complained of non-specific symptoms, such as gynecological disorders (pain, menorrhagia), but also wide-ranging extra-pelvic symptoms (persistent asthenia and fatigue, heart palpitations, tinnitus, pruritus, joint and/or muscle pain, skin rashes, digestive disorders…) [3].

Parent and collaborators [9] report a significant correlation between the concentrations of nickel (Ni) and chromium (Cr) in fallopian tube tissue and peritoneal fluid, suggesting a diffusion of these implant metal complexes in the body. However, no clear relationship was found between the three main symptoms reported (fatigue, psychological disorders, or joint pain) and levels of Ni and Cr metal elements [9].

The present study shows that in the control group, all Chromium and Nickel concentrations in the hair (25/25) were below the quantification threshold (1 µg/g), while 1/25 for Chromium and 2/25 for Nickel were between the detection and quantification limits (0.1µg/g < Cr or Ni present though not quantifiable <1 µg/g).

All the included subjects (10/10) presented a polysymptomatic clinical picture associating at least 3 persistent and treatment-resistant complaints.

Despite the presence of chromium and nickel in all implanted poly-sympathetic patients, there is no correlation between the number of symptoms and the concentration of these two metals in the hair (Table 4).

Furthermore, analyses of the implant's uterine biopsy parts show that stannic particles were found most often in the samples. In addition, all analyses of used implants showed a significant level of degradation, with a destructive aspect of the tin solder and the presence of organic tissue around the damaged weld, as well as a spread of tin particles inside the organic tissue [4,10]. According to the authors local inflammatory lesions associated with the presence of tin particles may explain the pelvic pain and dyspareunia reported by patients and the bioproduction of organotins after

tin leaching and corrosion could induce some systemic symptoms [10]. In this context, tin dosing in the implanted patients becomes crucial. However, except the mineral analysis from the excisional biopsy, there are currently no validated analytical criteria for monitoring the tin release and its impregnation for these patients.

In animals, the biodistribution study of the intraperitoneal stannous chloride administration has shown tin main localization in the bone, although the liver, kidneys and spleen also show concentrations slightly higher than the whole-body average during the first 80 days following the injection [11]. In the case of repeated subcutaneous doses of radioactive stannous chloride ^{113}Sn, about 60% of the tin ^{113}Sn is retained in the body and about 95% of this amount accumulates in the skin and hair [12].

In this context, the hair analysis of metallic elements is crucial because hair is the best matrix to reveal tin long-term exposure. Indeed, with a growth rate of about 1 cm each month, a 3 cm hair sample reflects the average levels of inorganic pollutants over the previous 3 months [13].

In the present study in the group of control subjects, 25 assays were below the quantification threshold (0.1 µg/g) and 2/25 are between the detection and quantification limits (0,07µg/g < Tin present although not quantifiable <0,1 µg/g).

In the implanted group, the presence of tin was demonstrated in all the patients (concentration >0.07 µg/g) while 8/10 were above the quantification threshold.

The mean tin concentration in implanted patients was significantly higher than in controls: 0.25 ± 0.17 µg/g vs. 0.007±0.005 µg/g, $p<0.003$.

For dosages above the quantification threshold (>0.1 µg/g), The hair tin concentration is proportional to the duration of device implantation (correlation coefficient of 0.79) (Table 4). Figure 1. represents the modeling curve of the tin concentration as a function of the implantation time, the equation of which is the following: [Concentration]=0.089 t – 0.325.

Similarly, above the limit of quantification, there is a positive correlation of 0.79 between the duration of Essure® implantation and the multiplicity of symptoms (Figure 2). This could partly explain the lag of several years between the commercialization of Essure® and the sudden increase in reports of adverse effects noted by some authors [4,14].

5. Conclusion

Tin seems to be an important factor involved in the physio pathogenesis of extra pelvic symptoms in patients with the Essure® medical device. In this context, the hair tin analysis is a useful tool in the monitoring of patients with Essure® implants. This analysis can allow the estimation of the impregnation of tin and to guide the etiological diagnosis of implanted patients suffering from extra genital disorders. Other work involving more patients is in progress.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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