Traitement Hormonal Thyroïdien. Où en est-on en 2019 ?

Milou-Daniel DRICI

CRPV Nice-Alpes-Côte d'Azur

Déclaration d'intérêt : aucun conflit avec cette présentation

- ANSM :
  - Gpe de travail cardio-thrombose
  - CT pharmacovigilance
- EMA :
  - SAG Cardio
- DSMB (aucun financement personnel)
  - SANOFI

Levothyrox®

Estimation incidence hypothyroïdie avérée

F = 4/1000 et H < 1/1000 (SFE-HAS 2007) ***(200 000)***

0,1 à 2% des adultes (Rev Prescrire 2015) ***(1.4 M)***

Estimation du nombre de patients sous levothyroxine

2,6 millions… 3,9% de la population française

Dose journalière estimée

100 µg/j

https://ansm.sante.fr/var/ansm_site/storage/original/application/7181268ac5a247ed769ea6b961d21232.pdf

Traitement idéal de l'Hypothyroïdie…

La lévothyroxine est indiquée dans les hypothyroïdies ou dans les circonstances, associées ou non à une hypothyroïdie, où il est nécessaire de freiner la TSH. Les situations où la TSH doit être freinée sont les goîtres, les nodules et les cancers thyroïdiens différenciés.

https://ansm.sante.fr/var/ansm_site/storage/original/application/7181268ac5a247ed769ea6b961d21232.pdf

Le traitement par lévothyroxine ne doit pas être initié sans qu'il ne soit réalisé au préalable au moins un dosage de TSH. En cas d'hypothyroïdie, si le taux de TSH est supérieur à 10 mUI/L lors de 2 examens successifs, un traitement par lévothyroxine doit être discuté avec la personne. Le dosage de la TSH est recommandé 6-8 semaines après le début du traitement par lévothyroxine ou après tout changement de dose ou de spécialité.

https://www.has-sante.fr/portail/jcms/c_2910740/fr/pertinence-des-soins-hypothyroidie

On utilise la LT4: Lévothyrox®. Les valeurs normales de la TSH sont < 4 mUI/L, et les objectifs de traitement se situent entre 0,4 et 2,5 mUI/L (sauf certaines pathologies). Dans tous les cas, il faut éviter le surdosage, du fait des risques osseux et cardiovasculaires de la thyrotoxicose.

http://www.sfendocrino.org/article/399/item-248-ndash-hypothyroidie

Constat

- ↑prévalence
  - 3,03 % en 2006
  - 4,10 % en 2012 (35 %)
- vieillissement de la population (hypothyroïdies iatrogènes?)
- traitement initié
  - généraliste (88%),
  - *endocrinologues (9 %) »*
- ~10 % thyroïdectomie et ~ 30 % de patients sans dosage de TSH remboursées préalables.

https://ansm.sante.fr/var/ansm_site/storage/original/application/7181268ac5a247ed769ea6b961d21232.pdf

Levothyrox® AF & NF

	LEVOTHYROX ancienne formule	LEVOTHYROX nouvelle formule
Nom commercial	LEVOTHYROX®	LEVOTHYROX®
DCI	Levothyroxine sodique	Levothyroxine sodique
Excipients	*Lactose monohydraté*, amidon de maïs, gélatine, croscarmellose sodique, stéarate de magnésium	*Mannitol*, amidon de maïs, gélatine, croscarmellose sodique, stéarate de magnésium, *acide citrique anhydre*
Forme pharmaceutique et dosage	Comprimés de 25 µg à 200 µg sécables	Comprimés de 25 µg à 200 µg sécables
Classe pharmacologique	Médicaments de la thyroïde (code ATC : H03AA01)	Médicaments de la thyroïde (code ATC : H03AA01)
Indication(s)	Hypothyroïdies. Circonstances, associées ou non à une hypothyroïdie, où il est nécessaire de freiner la TSH.	Hypothyroïdies. Circonstances, associées ou non à une hypothyroïdie, où il est nécessaire de freiner la TSH.
Condition de prescription et de délivrance (France)	Liste II Remboursé à 65 %.	Liste II Remboursé à 65 %
Procédure d'enregistrement *(pays rapporteur et co-rapporteur si procédure européenne)*	Nationale	Nationale
Titulaire d'AMM / Exploitant	Merck Santé	Merck Santé
Date d'obtention de l'AMM	02/06/1980 (50 µg) 08/02/1982 (100 µg) 26/01/1988 (25, 75, 150 µg) 09/02/1999 (125, 175, 200 µg)	27/09/2016
Date de commercialisation en France	02/05/2000 pour les AMM les plus récentes	A partir du 27 mars 2017
Pays commercialisant la (les) spécialité(s)	Pays de l'union européenne	France

Remplacement du Lactose monohydraté par du mannitol et de l'acide citrique anhydre

stabilité plus importante de la LévoT tout le long de la durée de conservation du médicament

https://ansm.sante.fr/var/ansm_site/storage/original/application/7181268ac5a247ed769ea6b961d21232.pdf

Spontaneous adverse event notifications by patients subsequent to the marketing of a new formulation of Levothyrox® amidst a drug media crisis: atypical profile as compared with other drugs

doi: 10.1111/fcp.12446

ORIGINAL ARTICLE

Spontaneous adverse event notifications by patients subsequent to the marketing of a new formulation of Levothyrox® amidst a drug media crisis: atypical profile as compared with other drugs

Delphine Viard, Nadège Parassol-Girard, Serena Romani, Elise Van Obberghen, Fanny Rocher, Sofia Berriri, Milou-Daniel Drici*

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Viard, D., N. Parassol-Girard, S. Romani, E. Van Obberghen, F. Rocher, S. Berriri and M. D. Drici (2018). "**Spontaneous adverse event notifications by patients subsequent to the marketing of a new formulation of Levothyrox((R)) amidst a drug media crisis: atypical profile as compared with other drugs.**" Fundam Clin Pharmacol.

LEVOTHYROX® NF

- Notifications peu informatives (chronologie, biologie, comorbidités).
- enregistrées dans les bases transmises à l'OMS.
- Biais de détection : lors du retrait des déclarations françaises sur le lévothyrox de l'année 2017, 32 signaux ont pu être identifiés.
- 1ère observation d'un biais national impactant une base mondiale.

L'impact de « la crise du levothyrox en France » sur la détection de signal sur la base de données de pharmacovigilance de l'OMS

Received: 11 May 2018 | Revised: 7 September 2018 | Accepted: 28 September 2018
DOI: 10.1002/pds.4682

LETTER TO THE EDITOR

WILEY

Impact of the "French Levothyrox crisis" on signal detection in the World Health Organization pharmacovigilance database

Recently, Klein et al described and assessed the influence of precautionary reports (systematic recording of often unrelated events in pharmacovigilance database through, for example, organized data collection systems) in the Dutch adverse drug reaction database.[1] They showed that these precautionary reports produced a competition bias, which significantly modifies the drug safety profiles, creating spurious associations and masking signals. A competition bias occurs when reports associated with a drug-event pair hamper the detection of disproportionality signals associated with the other drugs or events.[2] Overall, exclusion of these reports improved the quality of signal detection in their pharmacovigilance database.

Recently, the French pharmacovigilance centers received a huge number of "often unrelated" adverse drug reactions following the reformulation of levothyroxine pills.[3] Most reports were spontaneously reported by patients, in a context of a widespread media coverage, through a web-based application setup by the French health authorities. The vast majority of reports were of poor quality, lacking chronological or biological information needed to accurately assess causality.[4] However, the lack of available data did not allow to rule out the link between the reported adverse events and the Levothyrox. Thus, according to the guidelines of good pharmacovigilance practices all spontaneously reported events, even if the relationship is unknown or unstated, have to be considered as adverse events; therefore, these reports were recorded in the French national database and transmitted to the World Health Organization (WHO) pharmacovigilance database[5] Vigibase®. These reports therefore present similarity with the precautionary reports described by Klein et al. To assess the impact of these reports, we calculated the number of positive signals of disproportionate reporting (SDR) before and after excluding the French reports associated with levothyroxine since the beginning of the "crisis" (January 2017).

In a didactic purpose, we studied the strongest levothyroxine signal in Vigibase®, "diffuse alopecia," and we analyzed drugs considered as "suspect." Disproportionality analysis was performed using the reporting odds ratio (ROR). The cutoff for signal detection was defined as a ROR lower boundary 95% confidence interval greater than or equal to 1 and a number of cases (n) greater than or equal to three, according to the definition of the European Medicines Agency (EMA).[6,7]

On March 28, 2018, among the 65,519 individual case safety reports (ICSRs) associated with levothyroxine in Vigibase®, 26,840 had been reported by France since January 2017, representing 1% of total number of the reports received by Vigibase® during this period. 99.8% of the 4,678 reports of diffuse alopecia contained in Vigibase® had also been reported by France during this period. Overall, 335 medicinal products were associated with diffuse alopecia in Vigibase®, and 10 were considered as SDR according to the EMA definition. After excluding the French levothyroxine ICSRs reported since 2017 from the database, 32 new SDR were unmasked (Table S1).

Moreover, the proportion of ICSRs needed to reach the threshold of signal detection for diffuse alopecia increased from three to eight on 10,000 ICSRs reported with a given drug, which will delay the future detection of adverse reactions.

This bias could also exist for other adverse events frequently reported with the new levothyroxine formulation in France, such as dizziness, headache, myalgia/arthralgia, and sleep or mood disorders.

Our study provides another example of a competition bias and highlights their negative impact on signal detection and on the effectiveness of the pharmacovigilance system. Moreover, this is the first observation of the worldwide impact of a national reporting bias. Precautionary or poor quality reports should be identifiable in pharmacovigilance databases, to allow stratified analysis.

ACKNOWLEDGEMENTS

We thank Dr Alison Foote (Grenoble Alpes University Hospital) for critically editing the manuscript. We also thank Uppsala Monitoring Center from providing us full access to Vigibase®.

DISCLAIMER

The data in Vigibase® comes from a variety of sources and countries. The likelihood of a causal relationship is not the same in all reports. The opinions and conclusions in this study are not necessarily those of the various centers of pharmacovigilance or of the WHO.

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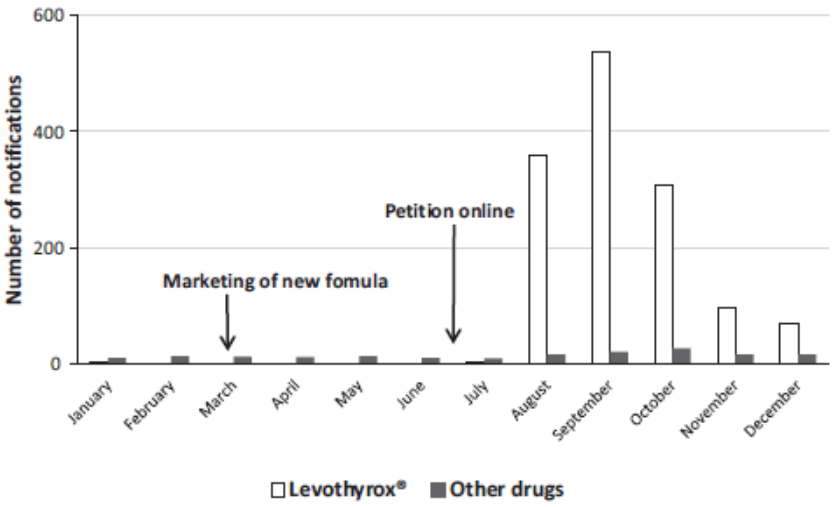
LEVOTHYROX® NF



CRPV de Nice : notifications patients relatives au Levothyrox®

doi: 10.1111/fcp.12446

ORIGINAL ARTICLE

Spontaneous adverse event notifications by patients subsequent to the marketing of a new formulation of Levothyrox® amidst a drug media crisis: atypical profile as compared with other drugs

Delphine Viard, Nadège Parassol-Girard, Serena Romani, Elise Van Obberghen, Fanny Rocher, Sofia Berriri, Milou-Daniel Drici*

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Fundamental & Clinical Pharmacology

Keywords
drug adverse events, levothyroxine, mass media, patient spontaneous reporting, pharmacovigilance

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ABSTRACT

Since patients may report spontaneously adverse events associated with their medications, such notifications are constantly on the rise. In 2017, an unexpected rise of notifications associated with the marketing of a new formula of Levothyrox, differing from the 30-year-old drug only by minor elements, occurred in France amidst widespread media coverage. Not much, if any, scientific or pharmacological rationale was identified to explain that signal. This led us to focus on the profile and the clinical characteristics of these notifications and compare them to those associated with other drugs. We gathered all the spontaneous drug adverse event notifications associated with either Levothyrox® or other drugs, that we received from patients in 2017, in the sanitary territory of ~2.3 M people we surveyed. Each notification was assessed by a multidisciplinary team. We compared the number of notifications, the number of symptoms described and their clinical characteristics. A total of 1 544 patient notifications were evaluated: 1 372 cases totaling 7 342 adverse events concerned Levothyrox® new formula, as compared with 172 cases reporting 528 adverse events for all other drugs. The number of symptoms reported per notification was significantly higher for Levothyrox® (5.4) than for other drugs (3.1, $P < 0.001$). Symptoms associated with Levothyrox® belonged to more System Organ Classes and were often unrelated to the disease or treatment, as compared with those associated with other drugs. The distribution of the cases according to the number of symptoms described was starkly different, the Levothyrox® distribution being unimodal. Health authorities must address this issue as such large atypical reporting disproportionally affects the European pharmacovigilance database.

INTRODUCTION

In France, over 2.6 million patients are treated with synthetic levothyroxine as a thyroxin replacement treatment for either hypothyroidism or circumstances requiring thyroid stimulating hormone (TSH) suppression [1]. Levothyrox® is an oral drug which contains sodium levothyroxine and has been marketed for over 30 years by the marketing application holder (MAH) Merck Santé (France).

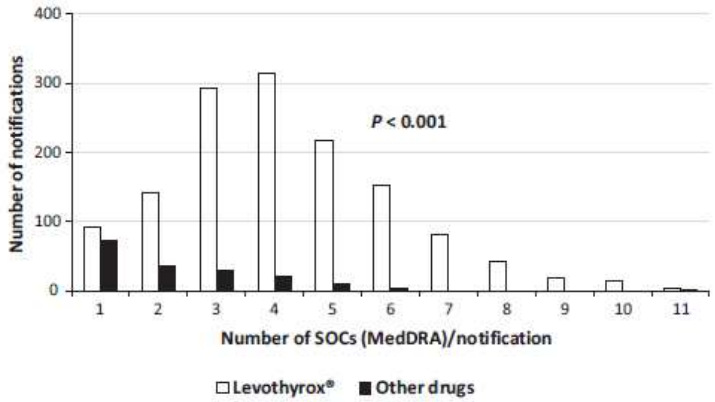
Recently, the French drug agency (ANSM : Agence Nationale de Sécurité du Médicament et des produits de santé) required the MAH to increase the stability of levothyroxine content throughout its 'duration of shelf',

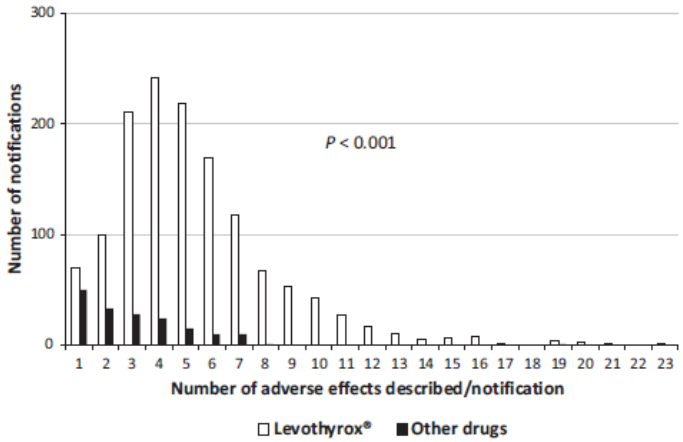
Le pic de notifications patient correspond avec l'emparement du sujet par les médias/réseaux sociaux/ personnalités

LEVOTHYROX® NF

Symptômes décrits > grand nombre de SOCs différents et sont souvent pauvres en infos en comparaison des autres notifications patients

Nombre de SOCs (System Organ Classes) par notification patient





Distribution du nombres d'effets indésirables par notification patient

Eventail de symptômes atypiques et nombre moyen d'effets indésirables par notification >> autres molécules

Spontaneous adverse event notifications by patients subsequent to the marketing of a new formulation of Levothyrox((R)) amidst a drug media crisis: atypical profile as compared with other drugs

Relevance of symptoms reported in each patient spontaneous notifications of drug-adverse events according to the SmPC of each drug or SmPC and main usual medical references

References	Levothyrox® (n=7342)		Other drugs (n=528)		P
	Relevant	Non relevant	Relevant	Non relevant	
SmPC	2286 (31.1%)	5056 (68.9%)	348 (65.9%)	180 (34.1%)	< 0.001
SmPC and other medical references *	4878 (66.4%)	2464 (33.6%)	384 (72.7%)	144 (27.3%)	0.004

* Other medical references : the Merck Manual®, the Harrison's Manual of Medicine®, and the Goodman and Gilman's® Principle of Therapeutic

Viard, D., N. Parassol-Girard, S. Romani, E. Van Obberghen, F. Rocher, S. Berriri and M. D. Drici (2018). "**Spontaneous adverse event notifications by patients subsequent to the marketing of a new formulation of Levothyrox((R)) amidst a drug media crisis: atypical profile as compared with other drugs.**" Fundam Clin Pharmacol.


Merci
ABONNEZ–VOUS pharmacovigilance@chu-nice.fr
http://centre-pharmacovigilance-nice.fr



Espoirs et Déceptions de certains médicaments

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Université de Nice-Côte d'Azur

Aucun conflit d'intérêt avec cette présentation

Cette présentation ne représente en aucun cas la position officieuse ou officielle de l'ANSM ni de l'EMA

Badabang……

SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

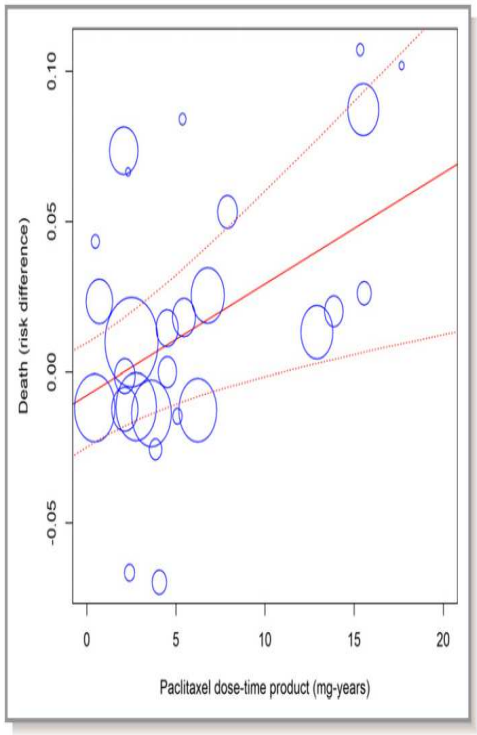
Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Clinical Trial Registration—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. (***J Am Heart Assoc.* 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.**)

Université Nice Sophia Antipolis — CRPV Nice Alpes Côte d'Azur

4663 patients



Study	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	RR	95%-CI	Weight (fixed)	Weight (random)
ZILVER-PTX [19]	19	297	7	177	1.62	[0.69; 3.77]	20.8%	20.6%
FINN-PTX [18]	1	23	0	18	2.36	[0.10; 54.68]	1.3%	1.5%
IN.PACT SFA [82]	16	198	1	106	8.57	[1.15; 63.70]	3.1%	3.7%
FEMPAC [29]	7	45	3	42	2.18	[0.60; 7.88]	7.4%	8.9%
LEVANT I [27]	4	49	5	52	0.85	[0.24; 2.98]	11.5%	9.4%
LEVANT II [26]	21	278	7	140	1.51	[0.66; 3.47]	22.1%	21.4%
CONSEQUENT [30]	2	70	1	65	1.86	[0.17; 20.00]	2.5%	2.6%
ILLUMENATE EU [32]	13	199	3	59	1.28	[0.38; 4.36]	11.0%	9.9%
ISAR-STATH [51]	3	48	1	107	6.69	[0.71; 62.66]	1.5%	2.9%
ISAR-PEBIS [55]	3	28	0	29	7.25	[0.39; 134.09]	1.2%	1.7%
ACOART I [40]	8	96	6	95	1.32	[0.48; 3.66]	14.3%	14.2%
IN.PACT SFA JAPAN [41]	4	66	1	29	1.76	[0.21; 15.05]	3.3%	3.2%
Fixed effect model		**1397**		**919**	**1.84**	**[1.27; 2.68]**	**100.0%**	--
Random effects model					**1.68**	**[1.15; 2.47]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.80$

Figure 2. Random effects forest plot of all-cause death at 2 years. Pooled point estimate was expressed as risk ratio (RR).

Study	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	RR	95%-CI	Weight (fixed)	Weight (random)
THUNDER [57]	12	48	8	54	1.69	[0.75; 3.78]	23.9%	26.9%
ZILVER-PTX [9,19]	42	297	12	177	2.09	[1.13; 3.85]	47.7%	46.3%
IN.PACT SFA [10,56]	24	184	7	103	1.92	[0.86; 4.30]	28.5%	26.8%
Fixed effect model		**529**		**334**	**1.94**	**[1.28; 2.96]**	**100.0%**	--
Random effects model					**1.93**	**[1.27; 2.93]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.92$

Figure 3. Random effects forest plot of all-cause death at 4 to 5 years. Pooled point estimate was expressed as risk ratio (RR).

Recommandations FDA (18.03.2019)

- Monitorer soigneusement les patients ayant bénéficié des ballons ou DUS au paclitaxel
- Le signaler au patient (consentement informé)
- Discuter le bénéfice/risque des alternatives en les favorisant jusqu'à nouvelle analyse
- Chez certains patients à haut risque de resténose, les praticiens peuvent malgré tout considérer le B/R positif de tels dispositifs
- Traitement médicamenteux optimal et des facteurs de risques +++(tabac, poids, exercice)

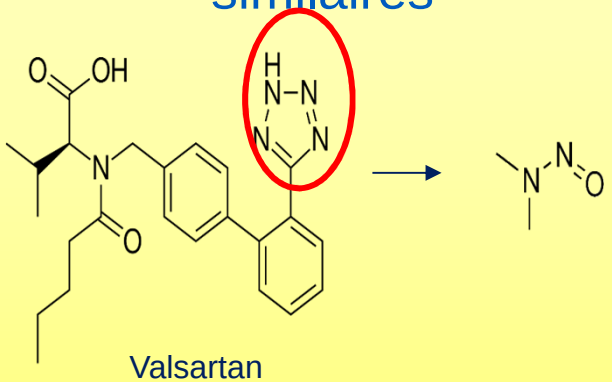
Les Sartans

- **Juillet 2018** : Rappel de tous génériques « valsartan » produits en Chine par Zhejiang Huahai Pharmaceuticals.
  - Découverte d'impuretés potentiellement cancérigènes > limites EMA.
    - N-nitrosodiméthylamine (NDMA) et N-nitrosodiéthylamine (NDEA)
  - Hypothèse : nitrosamines depuis 2012 (modif fabrication).
  - Leur dosage n'était pas demandé en routine.

Septembre 2018

Enquête élargie aux autres Sartans

Procédés de fabrication similaires



Valsartan
NDMA

Poursuite des rappels de lots

Novembre 2018:
Valsartan Mylan® (India)

Janvier 2019 : Irbésartan Arrow®.

Mars 2019 : Losartan Accord®

Décision EMA

Révision par les laboratoires de tous les processus de fabrication pour éviter la présence de nitrosamines (NDMA, NDEA, EIPNA, DIPNA, NMBA)

Les Sartans….

“Le risque de cancer est considéré comme faible »

« ~1 patient sur 5 000 en cas de prise de valsartan contenant l’impureté à la dose la plus élevée (320 mg) tous les jours de juillet 2012 à juillet 2018 »

-EMA. Update on review of valsartan medicines: risk from NDMA remains low, a related substance NDEA also being investigated. September 2018
-Pottegard A, Kristensen K, Ernst MT, Johansen NB, Quartorolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ 2018;362:k3851

Préviscan® plus d'initiation de traitement !

- 1er décembre 2018 : fluindione restreinte au **renouvellement des patients équilibrés**
  - E. I. immuno-allergiques plus fréquents qu'avec les coumariniques (warfarine et acénocoumarol).
    - *rénaux (atteintes tubulo-interstitielles)*
    - *hépatiques (hépatite)*
    - *hématologiques,*
    - *cutanées (DRESS)*

Ansm: Traitement par antivitamines K (AVK) : nouvelles informations - Lettre aux professionnels de santé. Novembre 2018

IEC et cancer du poumon

- Augmentation du risque cancer du poumon de 14% par rapport à l'utilisation d'ARA II
  - Hypothèse : accumulation de bradykinine et de la substance P au niveau pulmonaire.
  - Cohorte de 992.061 patients - suivi moyen de 6,4 ans.
  - Incidence brute de 1,3 pour 1.000 p/a.
  - ↑du risque avec durée d'utilisation
    - > 5 ans : + 22%
    - >10ans : + 31%

Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018 Oct 24;363:k4209.

Les Oméga-3

Oméga-3 prévention post-IDM?

Association/Society	Therapeutic Guideline	Omega-3s
ESC/EAS 2016 Cardiovascular disease prevention	Prevention of: - All cause coronary heart disease (CAD) - Stroke mortality	Questionable effect
ESC/EAS 2016 Management of dyslipidaemias	Prevention of cardiovascular disease after a cardiovascular event	Not recommended
ESC 2017	After acute MI in patients with ST-segment elevation	Diet recommendation but no supplementation
ACC/AHA 2013	Management of blood cholesterol to reduce atherosclerotic CV risk	Recommended in patients intolerant to statins
AHA 2017	Prevention of Coronary Heart Disease	Recommended

Ondexxya®-andexanet alfa

- New England Journal of Medecine, 7/02/2019

CONCLUSIONS

In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours, as adjudicated according to prespecified criteria. (Funded by Portola Pharmaceuticals; ANNEXA-4 ClinicalTrials.gov number, NCT02329327.)

andexanet alfa -

- Ondexxya® 200 mg, poudre pour solution pour perfusion, réservé à l'usage hospitalier
- *produit par des techniques d'ADN recombinant à partir de cellules CHO (Chinese Hamster Ovary).*
- Indication thérapeutique
  - adultes traités par un Xa (apix ou rivarox) lorsqu'une réversion de l'anticoagulantion est nécessaire (hémorragie incontrôlée, menaçant le pronostic vital).

Abonnez-vous pharmacovigilance@chu-nice.fr

M.D. DRICI

Université Nice Sophia Antipolis