State of the knowledge about the side effects of Roaccutane (isotretinoin):

abstract of a review of the scientific literature

Authors: many contributors, past, present, and future,

Opensource

Year: since 2005, to complete, correct, and enrich...
Thanks :

A big thank-you,

to all those who, from near or far, directly or indirectly, past, present and future, participate in the research and / or dissemination of information to all,

on a problem of public health, still too neglected in 2018,

which deserves, at least, that independent researchers be commissioned,

and ideally, that a new nosological entity be created:

for example, "exogenous isotretinoin intolerance syndrome (AR 13-cis)" ,

with all subclasses and nosological precisions (ranging from acute syndrome to absence of syndrome) that implies.

A special thanks to the author Max, from the forum http://max001.proboards.com/ , who has initiated this information movement in 2005 ...

The entire site is in PDF format:

He says (see Annex 4): "Thank you for bringing this information to people with biochemical skills / specialists in the field where your symptoms are most pronounced for clarification and correct interpretation. "

Everyone is free to enrich, complete, and correct this very short summary version, with here only:
the translated summary, dated 2005, and annexed,
the link to a statistical study, the table of contents of the PDF translated into French, and the list of abbreviations in biochemistry for an easier reading.

The PDF in English is being verified, updated and translated.

Thank you for sharing your contributions.

In memory of all past and present dramas, and to come if nothing changes on the part health authorities (see Annex 2: Statistical studies, pharmaco-epidemiological studies of the risk of depression related to isotretinoin).

For the HEALTH, and for Hippocrate.
Abstract:

Part of the effects of Roaccutane on the body:

Roaccutane is a form of vitamin A.

- Roaccutane and the receptors of nuclear hormones:

(Ro)accutane is a form of the fat soluble vitamin A that is termed a vitamin, but is classified as a steroid, and is administered to human acne-subjects in a 40-100 times overdose(*), and this during several months. Metabolites of (Ro)accutane, massive doses of retinoids, that are more active forms of vitamin A, affect hormonal receptors. The retinoid metabolites of (Ro)accutane are found to affect retinoid receptors, by the high binding-affinity for vitamin A isoforms, but also a large number of other hormonal and non-hormonal receptors are found to be affected [1]. These affected hormonal nuclear receptors and other non-hormonal affected receptors are widely expressed in different cell types all over the body, in nearly every single organ, including in several parts of the human brain [10]. This is likely the reason why retinoids (Roaccutane) are used for severe diseases such as prostate cancer, leukaemia [9], glioblastoma [8] (a form of brain cancer) and other areas.

(*) Recommended daily intake of 800 micrograms / day of vitamin A by European standards for food and nutrition; 25mg to 60mg for Roaccutane.

Today (as of July 2005), (Ro)accutane exposure, often in very young adolescent human subjects, is part of current dermatological practise. The skin is one of many organs that have cells that express retinoid and other nuclear hormone receptors [7]. The effects are many and one effect is that the metabolism or the cell division and proliferation is significantly reduced by significant hormonal suppression (simplified, the rate by which cells use energy is reduced). (Ro)accutane is also known to induce apoptosis, or programmed cell death [9]. This occurs in several parts of the body. In one part of the brain (the orbitofrontal cortex) the metabolism is found to be reduced by a mean of more than 20% in human subjects after four months of (Ro)accutane exposure [5].

Several deficiencies occur after exposure. Some which are measured in human subjects exposed to (Ro)accutane, including thyroid deficiency [2], androgen deficiency [3], vitamin D deficiency [4] and vitamin A deficiency. The fat metabolism is altered. In rats exposed to isotretinoin the insulin sensitivity in peripheral tissue was found to be significantly decreased [11].

Insulin production and release are with highest certainty significantly affected, due to the structure of the insulin receptor and the retinoid interaction with pancreatic beta cells. Even the growth hormone axis is linked to activity of the nuclear receptors and vitamin A, because the retinoid receptors are found to be expressed in somatropes, the cell type that produces growth hormone [6]. The hormonal effects are wide, and even more effects that are difficult to measure, or haven’t been clinically measured in public studies are suggested. Almost all hormones have receptors in cells in the brain, where they insert actions that are not fully discovered.

please see section 2.

It is not speculative to say, that these receptors are not designed for a 40 to 100 times overdose of any hormone, as the doses of (Ro)accutane exert.

The retinoid receptors (RXRs, RARs), the thyroid receptors (TRs), the androgen receptors
(AR), and the fat metabolism regulating PPAR receptors belong to the large superfamily of nuclear hormone receptors (NHRs), found in the nucleus of the cell, that regulate gene transcription [1]. It is not fully known what happens with these receptors, after a four month exposure of massive doses of (Ro)accutane.

- **(Ro)accutane induced hypothyroidism**

In human acne-subjects exposed to (Ro)accutane, levels of thyroxine and triiodothyronine were significantly lower after exposure (p less than 0.05), indicating a (Ro)accutane induced clinical thyroid deficiency (hypothyroidism) [2].

- **(Ro)accutane is strongly antiandrogen**

Roaccutane is strongly antiandrogen. A 50% suppression of androgen conversion rates have been found in related doses to what is seen in acne-subjects. The 5-alpha reductase is genetic and dependant on androgen receptor polymorphism. Androgen receptors (AR) as well as thyroid receptors (TR) belong to the superfamily of nuclear hormone receptors where also the retinoid receptors belong. The androgen receptor (AR) is a ligand-activated transcription factor that recognises and binds to specific DNA response elements upon activation by the steroids testosterone or dihydrotestosterone [3].

- **Clinical observations of 1,25-dihydroxyvitamin D in human subjects exposed to (Ro)accutane**

A significant fall in the level of 1,25-dihydroxyvitamin D, and a significant increase in the molar ratio of 24, 25-dihydroxyvitamin D to 25-hydroxyvitamin D was found in human subjects after exposure to (Ro)accutane, indicating a (Ro)accutane induced significant 1,25-dihydroxyvitamin D deficiency [4].

- **(Ro)accutane induced decreased insulin sensitivity**

In all exposed rats, in 15 days, isotretinoin increased glycerol concentrations and decreased the insulin sensitivity of peripheral tissues [11].

- **Vitamin A is strongly related to adult CNS function**

Since retinoids penetrate easily into the central nervous system, the Neurotoxicity of Vitamin A in adults is possible during consumption excessive supplements [12]. In the brain, cerebellum and meninges, the rates of all-trans-retinoic-acid (ATRA) was comparable in synthesis, or exceeded the rates measured in the liver of rats [12]. In human subjects with acne, Roaccutane is received between 50 and 100 times the consensually recommended dose for taking daily vitamin A, which is 0.8 micrograms (*). Roaccutane is administrated to people prone to acne for several months, and if less than a week of ‘Roaccutane’ therapy is the equivalent of the normal dose for years, the cumulative dose represents a consumption for several decades of vitamin A. In recent studies, it has been shown that all humans who have participated in studies on Roaccutane shows significant metabolic changes in the brain, while the effects on the nervous system can be seen as a consequence predictable, not just a possibility. Neural stem cells (NSCs) regenerate automatically, these are the multiple potential cells that produce neurons, astrocytes, and oligodendrocytes in the nervous system. Unlike the
dogma that prevailed for a long time, neurogenesis occurs in particular areas of the brain adult, hippocampus and subventricular zone, and NSCs reside in the system adult central nervous system. Recent studies have shown that neurogenesis is increased in diseased brains, after stroke and brain injury traumatic, and that new neuronal cells are produced in injury, where they replace certain degenerated nerve cells [15]. We do not know the degree to which Roaccutane caused CNS effects with replacement by neural stem cells. It is not known if a partial replacement by cells neuronal strains after degeneration caused by exposure to Traumatic roaccutane in subjects with acne has a diminishing effect on NSCs remaining: if this is the case, it would cause more limited repair over the course of life.

- **Inhibitory effects are suggested over several neurotransmitters, including serotonin, acetylcholine, melatonin, norepinephrine** (norepinephrine), and other neuro- steroids:

The potential track for tracking the action of retinoids in depression includes the dopaminergic pathway, serotonergic or noradrenergic complex interaction between these neurotransmitter systems [12]. As seen in this chapter, signal neurotransmission systems in the human brain can be involved in mood and well-being and are affected in subjects exposed to Roaccutane (this point is reviewed in section 2.1-2.6).

- **Changes in metabolism are significant in acne measures on subjects exposed to Roaccutane:**

A 21% drop in orbitofrontal cortex metabolism in human subjects exposed to Roaccutane was observed. Brain function in adults has was measured with positron emission tomography at 18-F-fluorodeoxyglucose before and after 4 months of treatment with isotretinoin (N = 13) or antibiotic (N = 15). The brain metabolism decreased in the orbitofrontal cortex (21% decrease against + 2% for the antibiotic), a sector of the brain known to mediate symptoms of depression [5].

The suggested cell losses in the hippocampus are significant in subjects exposed to Roaccutane, and further losses in other areas can not not be excluded. In a mouse model, it has been shown that endogenous RA is produced by enzymes syntheses in the meninges active on the neurons of the hippocampus nucleus, chronic way (3 weeks) following exposure to a clinical dose of 13-cis-RA (Roaccutane) and may result in loss of hippocampus cells [13]. Of the similar effects occur in the subventricular zone of rats were observed experimentally.

In adult rat brains, retinoic acid and thyroid hormone are known to regulate the differentiation and proliferation of precursor cells in the area subventricular (SVZ) [16]. Similar effects in humans are extremely likely. The most affected and yet not described areas on the brain mammal, related to exposure to Roaccutane in a similar way is extremely likely. (Areas of the brain that can be affected are reviewed under the section 2.1.1-2.1.5).

- **Roaccutane strongly induces the interruption of the signaling retinoids and the modification of retinoid signaling:**

Retinoid signaling plays an important role in the function of the human brain developed. The components of the metabolic process have been identified for retinoids in adult brain tissues, suggesting that all-trans-retinoic acid (ATRA) is synthesized in particular regions of the human brain. The distribution retinoid receptor proteins in the adult nervous system is different from that observed during development; it is suggested that this retinoid signal goes, in all probability, have a physiological role in the adult cortex, amygdala, the hypothalamus, hippocampus, striatum and associated brain regions. Many specific neuronal genes contain protein recognition sequences retinoid receptors, and can be directly regulated by retinoids [12]. In adult rats, the expression of CRABP in specific populations of neurons brain suggests that RA sees its metabolism dramatically transformed into mature brains, and especially in neurons. In addition, the genetic basis of its specific expression in these brain areas is localized in the 5, the region regulator of this gene [14].

The interruption of the retinoid signal in rodent models indicates their involvement in the control of synaptic plasticity and associated erudition as well as in memory behaviors. The retinoid signal channel has also been involved in the pathophysiology of Alzheimer's disease, schizophrenia and depression. So in general, the data highlight the likely importance of sufficient nutrient Vitamin A for adult brain function and essential retinoid intake indicates therapeutic targets, original and potential for neurological diseases [12].

- **Vitamin A affects the immune defense:**

Vitamin A deficiency is associated with exacerbation of immunodeficiency, the levels reduced or poorly balanced lymphocytes, and deregulated antibody production. The Animal experiments have shown that a sufficient level of vitamin A is necessary for production of an effective antibody response [17].

- **The suggested deterioration of the effects of age:**
In pituitary GH1 cells, a decrease in the thyroid receptor peak beta-2 (TRbeta2) of 50-70% under Roaccutane was observed in subjects with acne [18]. TRbeta2 is found mainly in the pituitary gland and hypothalamus. The measured amounts of thyroid receptors (TRs) that are mRNA, alpha and beta subtypes are considered as indicators in the elderly, a vision age-related clinical hypothyroidism [2] and may consider worsening their age-related function during exposure of the thyroid gland in subjects Roaccutane. During and after exposure to circulating Accutane, which has the effect of inhibiting growth hormone is proposed here, the conditions of GH / IGF-1 are modified as we suggest, as well as in part the result of the inhibition of function [2], and the inhibition of the expression of TRbeta2 receptors [18] (the inhibition of pituitary cell receptor and thyrotropic and somatotropic more and more apoptosis), 9-cis retinoic alpha receptors (RXRalpha) and interaction with IGFBP-3 [19] already proposed. The effects on expressed GH / IGF-1 receptors during and after an exposure accutane (Ro) are not known. An effect is aggravated by the lack of partial growth hormone that is normal to a advanced age, by favoring the lowering of the circulation levels of GH-IGF, and increase with age, in the GH / IGF-1 axis changes experienced as decreased brain concentration of GH and IGF-1. This decrease related to changes in hormone levels impact system functions central nervous system as some age-related memory disorders [20]. Insulin-like growth hormone factor 1 (IGF-1) and growth hormone (GH) have been proposed for memory and cognitive performance. Both GH and IGF-1 affect the size and morphology of the central nervous system (CNS) during of development and modify the different characteristics such as the growth of neural cells, myelination, and cognitive performance [20].

- References :

(*) Recommended daily intake of 800 micrograms / day of vitamin A by European standards for food and nutrition; 25mg to 60mg for the Roaccutane.


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Annex 2

- Statistical, pharmaco-epidemiological studies on the risk of depression related to isotretinoin:

[Isotretinoin and the risk of depression in patients with acne vulgaris, Laurent Azoulay, University of Montreal, 2007]

Open access study link:
https://papyrus.bib.umontreal.ca/xmlui/bitstream/handle/1866/15672/Azoulay_Laurent_2007_these.pdf?Sequence=1

In fact, in a significant sample drawn from a database of 30,496 patients from Quebec who took isotretinoin from 1984 to 2003, the gross, short-term risk is 2.00 (95% CI = 1.03 to 3.89), and the medium or long term risk is 2.68 (95% CI = 1.10 to 6.48) ...

By analogy, this risk is close to the risk for a woman to develop a lung cancer when she consumes more than ten cigarettes a day or 20 according to the statistical samples [1].

[1] Table 1 (page 5). Risk Rates for Lung Cancer Deaths observed in men and women in six prospective studies, according to the amount of cigarettes smoked.
From the study: Scientific evidence linking tobacco use to lung cancer, Dr. Norman L. Jones, MD, FRCP, FRCP (C), Michael G. DeGroote School of Medicine McMaster University Hamilton, Ontario, June 2008.

http://www.wsiat.on.ca/tracitdocuments/mlodocuments/discussions/fsmoking.pdf

- Please read page 9 of the following link, extracted from the regulatory authority of UK drugs:
2.5 Association between acne and depression :
https://assets.publishing.service.gov.uk/media/5492db7ce5274a42900002f2/DSU2.pdf

"There is a lack of robust population-based studies comparing the frequency suicide and suicidal ideation in adolescents with and without acne. Such a study would be beneficial to help understand the role of acne, as well as treatments such as isotretinoin, in suicide."

So an impartial and independent reproduction of a study epidemiological and statistical analysis similar to that of Dr. Azoulay from 2007, in other countries, would have a major interest in anticipating the problems of public health care regarding iatrogenic depressions due to isotretinoin, in long term.
Annexe 3

Abbreviations used in the PDF

- List of abbreviations used, genes/receptors/enzymes significantly affected by (Ro)accutane. Alphabetical order. Hyperlinks to Genecards Database.

List under construction.

- Metabolites, general terms :

1,25(OH)(2)D(3) 1alpha,25-dihydroxyvitamin D(3)
9-cis-RA 9-cis-retinoic acid; a metabolite of (Ro)accutane
13-cis-RA 13-cis retinoic acid; the active compound in (Ro)accutane
ATRA all-trans-retinoic acid
AD Alzheimer’s disease
CHF Congestive heart failure
CVD Cardiovascular disease
GH growth hormone
IGF-1 insulin like growth factor 1
PD Parkinson’s disease

- Receptors :

AR androgen receptor
FXR farnesoid X receptor
GHR Growth hormone receptor
gp330 megalin
IGF1R Insulin like growth factor I receptor
IGF2R Insulin like growth factor II receptor
IL1R1 Interleukin 1 receptor type 1
IR insulin receptor
IRS1 insulin receptor substrate 1
LXR liver X receptor; isoforms
PPAR peroxisome proliferator-activated receptor; isoforms
RA retinoic acid
RAR retinoid acid receptor; isoforms
ROR retinoic acid related orphan receptor; isoforms
RXR retinoid X receptor; isoforms
TLR toll-like receptor
TR thyroid receptor; isoforms
TRK tyrosine kinase; isoforms

- Enzymes(binding proteins/genes) :

5-alpha-r 5-alpha-reductase
CRABP cellular retinoic acid binding protein
ERK
GGP gamma-glutamyltransferase
IGFBP1  Insulin like growth factor binding protein 1
IGFBP3  Insulin like growth factor binding protein 3
L-FABP  liver type fatty acid binding protein
LPL  lipoprotein lipase
FAS  fatty acid synthase
PKA  protein kinase A
PKC  protein kinase C
RBP  retinol binding protein
RoDH-4  retinol dehydrogenase-4
SERT  
SOCS-1
SREBP-1  sterol regulatory element binding protein-1
TRK  tyrosine kinases, isoforms

- Transcription factors :

  AP-1
  AP-2
  NF-kappaB  nuclear factor kappa B
  NF-Y  nuclear factor Y
  SP-1  stimulatory protein 1
  SP-3
  STAT5A  Signal transducer and activator of transcription 5A
  STAT5B  Signal transducer and activator of transcription 5B
  TNF-alpha  tumour necrosis factor alpha
- Message from Max:

"Thank you for your feedback.

Please browse all sections of the PDF if you want to know which are the studies that are publicly available and that are done on retinoids and the brain.

You suggest a more user-friendly PDF.

I could very well add a section written in simplified language. However, there is a goal to show a greater spectrum of complexity, first the communication with the people in these scientific fields represented, and secondly, in order to show to any person with limited biochemical knowledge, that RoAccutane is a substance with very extensive and complex effects.

Thank you for bringing any information to a person with skills biochemists / specialists in the field where your symptoms are most pronounced for clarification and correct interpretation.

Sincere friendships,

Max »