

A Perspective on Retinoids

By Desmond Fernandes MB, Bch, FRCS (Edin), a Plastic and Reconstructive Surgeon practicing in Cape Town and Consultant in Charge of the Cleft Lip and Palate Clinic at the Red Cross War Memorial Children's Hospital. Dr Des Fernandes initially trained as a Cardiac Surgeon and was part of Professor Christian Barnard's Team. Dr Fernandes has taken a keen interest in skin cancer since the early reports of the "ozone hole" over the Antarctic. As a result of his interest, he came to the conclusion that skin cancer and ageing wrinkled skin are simply two manifestations of the same disease. When he realized that there were no suitable products available to address the light-induced deficiency of vitamins A, C, E and beta-carotene in the skin, he created a factory specifically to make the "ideal cosmetic".

Vitamin A has a major function to protect us and has a particularly importance role in maintaining normal healthy skin. With the increasing dangers posed by a thinner ozone layer, skin cancer and photo-damage have become more common. Within the next decade or two, every person on the planet will be at risk of suffering significant photo-damage.

While sunscreens can give protection, the safety of the skin will depend to a large extent on adequate levels of vitamin A and other antioxidants in the skin. It is conceivable that a major public health programme could focus on replenishment of vitamin A in the skin. For this reason, we have to find a cheap and effective method of replacing vitamin A in the skin.

Retinyl palmitate, an ester form of vitamin A, offers us the most acceptable way of boosting cutaneous levels of vitamin A with the greatest compliance. However, fashion and science have concentrated on the active metabolites of vitamin A, or synthetic retinoids. Retinyl palmitate can ultimately be converted into every possible metabolite of vitamin A so that, when used topically at adequate dosage, it affords us the most acceptable and inexpensive method of vitamin A replacement.

Vitamin A is fundamentally one of the most important vitamins because it controls the growth and differentiation of all our cells, from the embryo through to full maturity. It seems to be a hormone derived from the diet and one that works in concert with other hormones, for example, thyroid and adrenal hormones. Its effects are most easily observed on the skin because that is the most visible organ of the body and this is the area on which I would like to focus my attention.

Vitamin A is usually found in our skin in low concentration but is absolutely essential for healthy skin. However, vitamin A is rapidly destroyed by exposure to light, so our skin develops a chronic, unrelenting deficiency of vitamin A that manifests as pigmented blotches, wrinkles, thin skin, and pre-cancerous lesions that eventually develop into skin cancer. All of this simply because the skin is not

kept at optimum levels of vitamin A. Less vitamin A is released from the liver in Winter compared to Summer.

This is most likely to be a feedback system to maintain health levels of vitamin A in the skin (1). Research is showing us that vitamin A plays a role in the prevention of skin cancer, but we need to know more about how to use it, and which form to use (2). I believe that in the next 10 to 20 years we will reach a state where topical vitamin A will be required for most of the world's population to keep their skin healthy. This will not be a simple cosmetic, but a preventative health measure. Some statisticians have warned that melanoma will occur in one of every 70 people born in 2000. We have to address this problem before these dreadful statistics become reality. Therefore, we need to prepare a preparation containing vitamin A that people will use regularly with ease and safety.

What is the Most Suitable Form of Vitamin A?

If you scan the literature on retinoids, you will be confronted by a conundrum: all the research focuses on retinoic acid and retinol and other complex retinoids and there seems to be no research on retinyl palmitate. This is paradoxical, because retinyl palmitate is the major form of vitamin A in the human body and skin (3). Surely, we need to understand retinyl palmitate and how it affects the skin and the body?

More than 90 per cent of the vitamin A that we eat comprises long chain fatty acyl esters of retinol (retinyl palmitate is the most common acyl ester), which are the most stable forms of vitamin A. That must be why they make up more than 90 per cent of the vitamin A in our own bodies (4). Retinol is usually regarded as true vitamin A but it accounts for only a tiny fraction of the vitamin A in the body. It is also not the form of vitamin A that works on the DNA. Retinoic acid is another molecule regarded as "true" vitamin A, because it is the form that works on the DNA. However, retinoic acid also forms only a tiny fraction of the body's vitamin A.

Esterase enzymes initially act on retinyl esters which are hydrolysed to retinol, which is then oxidized by alcohol dehydrogenase to retinal and finally retinoic acid (5-9). There seems to be a feedback mechanism whereby retinoic acid production is controlled by increasing or decreasing the esterification of retinol (10) to retinyl palmitate (11). There are stereoisomers of retinol and retinoic acid and their metabolites which play important roles.

Various isomers may in fact have various effects on DNA – for example, one may control sebaceous secretion more effectively than another. The formation of these isomers requires energy and it is believed that the energy required for the production of the isomers may well come from the deesterification of retinyl palmitate which is the high energy molecule. Of course, we need to know what actually happens, but I believe that research workers concentrate on deciphering

exactly what these more recently defined “active forms” do, without giving any thought to retinyl palmitate, because retinyl palmitate is an “old molecule. Because vitamin A is stored as retinyl esters, they are actually the fountainhead of all the other active forms.

The esters of vitamin A seem to have a pivotal role in metabolism even though they themselves are not the active forms of vitamin A. In human skin, topically applied retinyl palmitate has been clearly shown to be hydrolysed to retinol, so retinyl palmitate is a very suitable method for cosmetic formulations to deliver retinol into the skin (12).

Retinyl palmitate has a poorly appreciated but central role in maintaining healthy skin cells and reducing the chances of cancer. For example, squamous skin cancer cells have an impaired ability to esterify retinol (13). We need to extrapolate on the many studies that have shown that retinyl palmitate promotes healthier skin (14-26).

Vitamin A is the dominant vitamin of the skin because it has a fundamental role in the control of normal activities of DNA in the nucleus, as well as the mitochondria. Current scientific research work is uncovering the complex means by which DNA maintains these normal activities. As early as 1938, it was pointed out that vitamin A deficiency probably developed in all areas exposed to sunlight (27). The reason for this is that vitamin A is extremely sensitive to sunlight and particularly to ultraviolet light A (UV-A) in the region of 334nm (28). A heavy sunburn radically depletes the cutaneous stores of vitamin A.

Cluver showed that people who suffered severe sunburn could be improved by oral administration of vitamin A in high dosage (1). Even with the development of modern sunscreens we are not able to give adequate protection of the skin from UV-A and so vitamin A is still damaged by exposure to light, even when a person is wearing a sun protection factor of 30 or 40.

“In the 1930s, it was postulated that skin exposed to sunlight aged faster than skin that was protected from sunlight. Once it was recognized that the deficiency of vitamin A caused by exposure to light is responsible for wrinkled, aged skin, the natural route was to see if administering vitamin A to the skin would reverse these changes. By 1955 it was discovered the application of vitamin A as retinyl palmitate rejuvenated aged skin to a small degree (29).”

The test period at that time was a mere six weeks. Today it is acknowledged that vitamin A is not only good for ageing skin, but almost essential (30), and rejuvenation can be achieved. The published literature would make you believe that only retinoic acid and retinol are the agents that can rejuvenate skin. This is far from the truth (31).

So, which forms of vitamin A can be used to maintain healthy, beautiful skin?

As I have pointed out, the most common form of vitamin A is retinyl palmitate. Vitamin A esters are milder on skin, still active and more easily tolerated. There are numerous esters of vitamin A (such as retinyl propionate and retinyl linoleate) but the most commonly used are retinyl palmitate and retinyl acetate. Retinyl acetate is a smaller and more active ester. Both of these esters are cheaper than retinol and retinoic acid and are significantly more stable. This ensures that compounded products maintain the targeted levels of vitamin A for longer. Research work has shown that retinyl acetate is at least as – or even more – effective (relatively) than retinoic acid (23), possibly because it penetrates the epidermis more efficiently than retinoic acid.

The importance of these particular cosmetic retinoid esters is that they give much the same results as the pharmaceutical form of retinoic acid, but are much less irritating on the skin; hence, patients are more likely to use them regularly. Interestingly enough, the proponents of retinoic acid have also shown evidence that lower doses of vitamin A acid in the long run have similar effects as maximum levels, but of course have fewer side effects (32). Voorhees and his co-workers have now even suggested that it might be preferable to use less aggressive forms of vitamin A to get the same results because patients tolerate it better (33).

Some people criticize retinyl palmitate for being weaker in its effects as compared to retinol and retinoic acid. One important fact to bear in mind is that the esters generally carry a very heavy chain (palmitate is $C_{16}H_{32}O_2$) in addition to the basic vitamin ($C_{20}H_{30}O$) molecule, so should not be compared weight for weight.

It is essential to compare their quality as represented by international units (i.u.) of vitamin A or even retinol equivalents (R.E.). By using 5000 i.u. retinyl palmitate for one to two years, it is possible to get similar results to those achieved by using retinoic acid 5000 i.u. for the same period. The difference, of course, is that the patients using retinyl palmitate will have significantly less irritation than the patients using retinoic acid. I believe the case for the equivalent status of retinyl palmitate, retinyl acetate and retinoic acid has been clearly demonstrated as far as basic skin changes are concerned, and retinyl esters should be used daily by everyone to maintain health skin.

Another reason for this is that it is the retinyl palmitate molecule that gets denatured by exposure to sunlight. So one would be replacing the precise molecule that is required. Retinal or retinyl aldehyde, which is absolutely essential for normal vision, has also been used to topical application because it oxidizes to retinoic acid. I believe that marketing forces will soon pressurize people into believing that this is the best cosmetic agent. No one seems to worry

that retinaldehyde is normally only found inside cells and not in the intercellular space. It is a metabolite of retinyl palmitate. Interestingly, beta-carotene can be absorbed into cells and broken down into two molecules of retinaldehyde.

Retinol is the alcohol form of vitamin A, and is currently the latest fad in cosmetics. This is the form of vitamin A that is normally used to transport vitamin A from the liver to the tissues. Some retinol is found free but most is bound to retinol binding proteins (RBP) in the bloodstream, then taken up by the various organs. In high doses, free retinol can be toxic to cellular membranes. Under normal circumstances, free retinol seems to be in balance with RBP retinol with only a minor percentage of retinol being free. Topical application of high doses of retinol may cause irritant symptoms because of this toxic effect on cellular membranes. Retinol is less irritant than retinoic acid but not nearly as kind to skin as retinyl esters.

Retinoic acid gained great popularity and also notoriety after the publication of Kligmann's work (34). This is the most irritant form of vitamin A (also known as tretinoin) and is usually only available on prescription. It is therefore not the best agent for topical administration of vitamin A to the vast majority of the world's population. Retinoic acid and retinol suffer from having short shelf lives, both as an ingredient and also as a compounded product. That means that products made with them rapidly lose their fullest vitamin A effects.

Beta-carotene is the plant version of vitamin A. Sometimes beta-carotene may be labeled as vitamin A; in fact, it is a pro-vitamin A and can be metabolized into two molecules of retinyl aldehyde. Beta-carotene is also a most powerful free radical quencher that is not matched by vitamin A. Estimates suggest that one beta-carotene molecule can cope with 1,00 free radicals. Beta-carotene counteracts the effects of the sun, whereas the sun destroys vitamin A.

Beta-carotene is only converted into vitamin A if there is a physiological need for vitamin A. Under normal circumstances beta-carotene is maintained as beta-carotene and is normally found in relatively high (though minute!) concentrations in the skin. Beta-carotene levels are higher in Oriental people than in Occidental people.

The Effects of Vitamin A on the Skin

“Mechanisms have to exist to facilitate the transfer of vitamin A from outside the cell wall through the membrane into the cell substance itself. There are receptors on the keratinocyte cell wall where vitamin A as retinol, retinyl palmitate, acetate or retinoic acid can enter into the cell. Once inside the cell itself – and probably only once it has entered the central nucleus with its DNA, or the mitochondrial DNA – can vitamin A produce changes to the skin.”

An interesting dilemma occurs in cells that have been exposed to sunlight: the retinoid receptors are damaged and so less vitamin A can be taken into the cell. Topical application of vitamin A stimulates the development of more retinoid receptors on the cell. The typical retinoid reaction of irritated, red, sensitive skin, seen particularly with retinoic acid and retinol, may well be from the damage to cellular membranes because the vitamin remains external to the cell instead of being in the cytosol.

Other effects include:

- It affects the genes of the cells so that the keratinocytes grow and look more normal. It increases the growth of the basal layer (growth layer) of skin cells, which may be the predominant reason for the thickening of the skin. Not only does the skin get thicker; it also heals faster because the cells are growing faster.
- Vitamin A improves the horny layer, so it makes the skin more resistant to environmental pollution (35).
- Melanin in keratinocytes becomes more evenly distributed.
- The production of melanin by melanocytes is generally reduced to the normal rate for the colour of the skin.
- The production of sebum is decreased in oily skin.
- Vitamin A supports and potentiates the Langerhans cells of the skin.
- After UV damage, vitamin A can “resuscitate” sunburn cells.
- It affects the fibroblast cells, the most important cell in the dermis, particularly the genes for the production of collagen. Healthier collagen is formed and unhealthy collagen is removed by enzyme activity (36).
- It increases the secretion of natural moisturizing factors by the fibroblast cells of the dermis into the space between the cells, allowing the skin to retain more water with some puffing out of the wrinkles. These natural moisturising factors filter up into the epidermis between the cells. Glycosaminoglycans are some of the chemicals created by the fibroblast to help retain moisture.
- The blood supply to the deeper layers of the skin is improved, which means that nutrition of the skin is improved. The skin also assumes a healthier colour.

Topical Vitamin A

Vitamin A is measured in international units (i.u.) per gram. The recommended effective doses are between 500 i.u. and 10,000 i.u. Anything less than 500 i.u. is generally of little value. Vitamin A should be used daily. If used during daylight hours it should be accompanied by anti-oxidant vitamins like vitamin C, E and beta-carotene, so that it is better protected from ultraviolet light. Vitamin A metabolism is strongly linked to vitamin C, which is essential for the proper function of vitamin E. The concept of the balanced use of these vitamins as the main way of maintaining skin health is becoming more and more certain with current research work. People should focus on the fact that our skin is constantly exposed to light, and light destroys certain essential chemicals in our skin. We can never escape this fact.

A reliable UV-A and UV-B sunscreen should be used at the same time in preference to a simple high sun protection factor (SPF) cream. There are no really effective UV-A sunscreens at this time except opaque zinc oxide. Therefore, vitamin A will always be damaged in skin even when using the highest sun protection factors. The damage might be less when using zinc oxide and titanium-based products, but the vitamin A will still be damaged. Vitamin A should also be replaced every evening as a topical application to the skin to try and address the loss of vitamin A through being in the light. Because we cannot prevent the damage to the vitamin A in the skin, it is essential to replace the vitamin A each day so that we do not gradually develop the signs of photoageing that are also the signs of accumulative vitamin A deficiency in the skin.

Professor Cluver was a pioneer in recognising that vitamin A played an essential role in counteracting sun damage (37). He showed that every time we are exposed to sunlight, the photosensitive vitamin A molecule is denatured not only in the skin, but also in the blood. We now know that UV-A rays, particularly at 334nm, are responsible for photodecomposition of Retinyl palmitate (38).

Paradoxically, retinyl palmitate is more photo labile than retinol (39). This is, I believe, a very powerful argument for replacing retinyl palmitate on the skin in preference to retinol, in order to address the retinyl palmitate deficiency of the skin.

If retinol is applied, it is more irritant and still have to be physiologically esterified into retinyl esters. Once the skin retinoids are depleted, it takes several days before diet alone can restore the normal cutaneous retinoids levels. Application of an active vitamin A cream can restore the normal vitamin A concentration within hours.

Is There a Danger in Over-Exposing the Client to Topical Vitamin A?

”Most doctors do not know the dynamics of penetration of vitamin A into the skin, and they are generally not informed about absorption of vitamin A from the dermis into the bloodstream. The truth of the matter is that cutaneous absorption is not efficient. The most effective penetration of any cream is only in the region of seven per cent, and two per cent is considered average”.

If you rub a gram of vitamin A cream containing 5,000 i.u. g% on the face then you will apply 5,000 i.u. on to the facial skin, and of that, up to a maximum of 350 i.u. will reach the keratinocyte layer or the upper papillary dermis over about 26 sq cms. This is approximately 1.2. i.u. per sq cm and this probably translates into a concentration of vitamin A in the tissues that is close to the serum concentration. Even if one uses a cream/gel with 10,000 i.u. the levels of vitamin A are still minimal. As it happens, epidermal levels of vitamin A (and beta-carotene) in the dermis are up to about 10 times higher than the serum levels. So it seems that there must be some active concentration of vitamin A in the skin against the osmotic gradient. It is fair to say that vitamin A is delivered from blood to skin and hardly at all from the skin to blood.

A reason for this is that skin blood vessels may not possess the enzymes necessary for combining retinol with serum retinol binding proteins. That is the main transport mechanism for vitamin A into the bloodstream. Using radioactive labeled vitamin A, research workers have found minimal traces of vitamin A in the blood, even when large areas were treated with retinoic acid. In practical terms, one can say that virtually no topically applied vitamin A is absorbed into the bloodstream under ordinary circumstances. It is extremely unlikely that topical vitamin A could ever pose a health risk, or a risk to pregnancy – unless the cream is taken orally! When people try to control or minimise serum vitamin A levels, they ought to focus on dietary vitamin A.

To understand dietary levels of serum vitamin A, consider the following statistics:

- One slice of liver (an average serving) contains about 20,000 i.u. for chicken liver, and up to 50,000 i.u. for beef or lamb liver.
- Kidney has 1,083 i.u.
- A chicken pie has about 1,200 i.u.
- Pro-nutro® - 125ml has 1,750 i.u.
- An egg contains 260 i.u. and also has beta-carotene
- Skimmed milk enriched with vitamin A has 1,000 i.u. in 125 ml
- A slice of lean meat contains 8 i.u.
- A slice of fatty meat contains 20 i.u.
- An éclair has about 1,500 i.u.
- Soft margarine has 3,335 i.u. in 125 ml

- Butter has about 300 i.u. in the standard, small, wrapped portion.
- Canned apricots have 2,900 i.u. (as beta-carotene)

What about the Dangers of Topical Vitamin A and Pregnancy?

A great deal has been written about the harmful effects of retinoids in pregnancy. Again, this danger is an extrapolation of the effects of retinol which rapidly crosses the placental barrier, and also cis-retinoic acid and retinoic acid (40), which can also, cross the barrier. Retinyl esters, on the other hand, do not pass through in any significant degree in humans (410).

I would like to add that in the US< it is becoming customary for manufacturers of vitamin A products (usually retinoic acid or retinol) to inform clients that while they do not believe that topical vitamin A can cause any foetal abnormality, they recommend that their clients do not use topical vitamin A during the first trimester of pregnancy. This is to avoid the mistaken attribution of any malformation to topical vitamin A.

Conclusion

Vitamin A, particularly as retinyl palmitate, is probably the safest way to protect the skin from solar irradiation and may also be used to rejuvenate skin if used for protract periods. The ideal treatment would be to apply topical vitamin A to the skin starting at an early age, soon after our first exposure to light, and continuing the daily replenishment of vitamin A into old age. Not only would this maintain young, healthy looking skin, but in all probability would also protect against cancer (42).

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