Coronavirus and chronic pain

First an important warning: this is <u>not</u> a scientific article. There are some underlying scientific facts, but these are not presented here in an orderly fashion. The list of scientific references is not exhaustive. This is a personal view based on the author's knowledge and experience, not medical advice.

This is an article about coronavirus and treatment options that may be theoretically possible. It appears on the page of chronic pain, because there are striking parallels between these treatment options and the treatment options of chronic pain. The term 'virus' could be replaced by 'chronic pain' in many places.

It seems a bizarre combination and a similarly bizarre brainwave. The present host of publications on coronavirus reports several elements: the virus attaches to receptors deep inside the lungs, where it causes a 'severe acute respiratory syndrome' (SARS). There is a lot of literature on SARS: Pubmed gives 9064 hits, free full texts 3362. But what exactly is SARS? It is an acute-onset condition characterised by high fever, coughing and dyspnoea, which can easily progress into more severe health conditions. Like influenza, coronavirus can cause severe pneumonia, myocarditis and damage to the central nervous system. This has a negative effect on the circulation and leads to fluid loss and decreased blood pressure.

I remember a remark by a professor of internal medicine when I was still training to become a doctor: *in case of an acute cardiac or pulmonary condition, administer an injection of calcium and an injection of euphylline* (generic name: aminophylline). This may seem too simple to be taken seriously, but it has saved the lives of a few patients in my practice.

Aminophylline is a scion of the Xanthine family, which also includes theophylline and pentoxifylline. In the Netherlands, theophylline is still used in pulmonary disorders, nowadays termed COPD. Pentoxifylline is used clinically to treat poor perfusion of the legs and laboratories use it for inflammatory-like conditions and shock. In 1977, two pharmacologists from Nova Scotia published studies with a substance which had been discovered in 1935 but could only be synthesised and used in pharmacological studies since the 1960s. The substance was referred to as prostaglandin. Prostaglandins are a group of substances that – on their own - do not have a biological effect in a preparation. They only have an effect in the presence of another biologically active substance. To illustrate this: take for instance a prostaglandin ('A') and a vasoconstrictive substance ('B'). Neither A nor B has any effect on its own. The combination A plus B, however, has a vasoconstrictive effect. Or if A is combined with vasodilator 'C': together they have a vasodilatory effect. This means that the effect of A is variable. 'A' determines the magnitude of the effect of B and C. This is a slightly simplified explanation of what actually happens.

Aminophylline is a bronchodilator, but it also acts on the heart. We know now that its cousin pentoxifylline improves the perfusion by means of enzyme inhibition. The energy released in this process is used to release or bind calcium ions. These are calcium atoms that have lost an electron. The ions are positively charged. Calcium ions are involved in a complex process in the cell which leads to the contraction or relaxation of muscle fibres. Muscle fibres around blood vessels will thus dilate or constrict the blood vessel. In addition, calcium ions also connect other structures to the cells and regulate the permeability of the cell. This is not just coincidence or course.

Pentoxifylline has another effect: it blocks some pro-inflammatory proteins such as TNF-alpha and

interleukin-6 and thus has an inhibiting effect on inflammations. Finally, as all xanthines do, it acts like a prostaglandin itself, probably because it inhibits specific prostaglandins when present in low concentrations and has the opposite effect in high concentrations. It will be evident that this can easily lead to conflicting research results.

Yet another substance pops up in the literature on coronavirus: treatment with chloroquine (an old antimalarial agent) is reported to have an inhibiting effect on the development of coronavirus (1,2,3,4,5). It is not clear whether this only concerns the clinical presentation or also the inhibition of virus production. There is one publication that concludes that virus production does not decrease (6).

Chloroquine belongs to the group of quinines, originally extracted from bark, like its predecessor aspirin (from different trees of course). What is the effect of these substances? Similar to xanthines, they are prostaglandin agonists and antagonists. Again prostaglandins. And they are active on many fronts. They play a demonstrated and undisputed role in inflammation and pain. Strikingly, the literature focuses mainly on details concerning the substances and viral structures, but not on why the virus is able to have such an impact. We need to see the big picture here. Let's recap the facts we have gathered so far:

There is a viral epidemic that causes inflammatory responses in the lower airways and can also cause myocarditis (inflammation of the heart muscle) and inflammation of the central nervous system. Without prostaglandins or without cytokines (pro-inflammatory proteins) there would be no inflammations of any kind. The very same prostaglandins transmit impulses to the central nervous system, which regulates the opening of ion channels in the cell wall, which may also stimulate the transport of the virus. In viruses containing a built-in injection system to transport RNA into the cell, the contractions of minute muscle fibres (myofibrils) play a role. The contraction force of these myofibrils is again determined by prostaglandins. So, prostaglandins as well as viral particles play an important role. How does this affect treatment?

Treatment and prostaglandins

Recent literature describes treatment with chloroquine as a potent inhibitor of coronavirus (1,2,3,4,5). What is the mechanism of action of chloroquine? It was already shown in 1977 that chloroquine was a potent inhibitor of prostaglandin as well as an imitator (antagonist and agonist). But the same was also demonstrated for quinine, quinidine, procaine, lidocaine and xanthine derivatives such as aminophylline, theophylline and pentoxifylline.

Quinine is extracted from the bark of the cinchona tree and has been used to reduce fever, to ease pain and to treat cardiac problems. Quinidine is mainly used in the treatment of arrhythmias (irregular heartbeat). These are also effects of prostaglandin, which is not surprising in view of the prostaglandin agonist/antagonist effect. There are also substances that inhibit the production of prostaglandins from cholesterol: aspirin, metamizole (known as Pyramidon, Novalgin, Nolotil and other names). Both substances are cheap and are frequently used around the globe, but banned in the United States and several European countries. In the Netherlands, it is not allowed to import or prescribe metamizole. It can only be prescribed by a doctor abroad and only be imported by the user himself in an opened package. The reasons for this cannot be explained scientifically (7,8,9).

Other substances, called corticosteroid hormones, such as cortisone, hydrocorticone and prednisolone, inhibit the production of prostaglandins in the cell walls. These substances are mostly used when the immune system kicks into high gear.

Procaine, lidocaine and similar substances are injected as a local anaesthetic. But these substances can also be injected directly into the blood stream. Procaine is successfully used to treat herpes zoster infections (shingles) in complementary alternative medicine. It has been known since 1977 that these drugs are prostaglandin agonists/antagonists, so their effect on viral infections is no surprise. It should be noted that these substances are not suitable for self-medication.

Finally, as mentioned above, there are the xanthine derivatives euphylline, theophylline and pentoxifylline. The latter, especially, is often used in animal experiments to treat inflammations after fractures, haemorrhages and bacterial infections. The mechanism of action of this drug has probably been researched most, compared with the other substances (Pubmed: 5300 hits). It is available as a drug to enhance the perfusion in the legs (in case of intermittent claudication), but it has also been known since 1977 to be a prostaglandin agonist/antagonist. More recently, it was found that they also inhibit pro-inflammatory proteins, or cytokines. They influence virus activity (10,11,12,13,14) even in SARS, although they do not seem to inhibit virus production (6). So, there is a whole series of drugs – known since 1977- that may inhibit or block the effect of a virus, and therefore also influence the effects of coronavirus. And these drugs are cheap and widely available.

What argues against using these drugs?

Chloroquine

Quinine derivatives, such as chloroquine have been removed from the repertoire of drugs, because they seemed to seriously deteriorate the disease in a number of hospitalised patients. This was of course not the intention. It is an unfortunate drawback, even though the drawback could be expected and explained. It has to do with the fact that, as described before, quinine-like drugs behave like prostaglandins. Prostaglandins have a characteristic that makes them effective, but that can also have a reversed effect. When used in high concentrations, the effect turns into the opposite. This is explained in more detail in an article about CRPS (16). It means that chloroquine can be expected to have an anti-inflammatory effect in the presence of a low concentration of cytokines (proteins that promote inflammation, produced as part of the inflammatory response), but have a pro-inflammatory effect in the presence of a high concentration of cytokines.

Theoretically, it can be expected that chloroquine has an inhibiting effect in the beginning of a viral infection, but not when administered in hospital patients with severe infections. It is therefore not surprising that it has an inhibiting effect in laboratory cultures but the opposite effect in hospital patients. It is supposed to be effective in the initial stages of an infection, but this has not been and will not be studied in further detail.

The same applies largely to remdesivir, in the sense that it has better virus-inhibiting properties in early stages of an infection than in the severe situations in which it is being used now, due to costs and availability, because remdesivir is also controlled by prostaglandins.

Many years ago, a short article was published in the Dutch journal of medicine (*Nederlands Tijdschrift voor Geneeskunde*) about a study of viral secretion from the nose after the patient had used aspirin for a common cold. According to the article, there were indications that aspirin would inhibit prostaglandin production but also stimulate the virus. It was only one publication, but an even rarer disorder was reported too: Reye's syndrome, a very severe, fatal disease that may develop after using aspirin in children with a cold. There is no 'hard' scientific evidence for this relationship either, but also in view of the other publication, it seems that aspirin is not suitable for experimental treatment of another viral disease. These observations can be explained, but the explanations also apply to other prostaglandin synthesis inhibitors. Metamizole is an exception, which can also be explained, but is not available in the Netherlands. Cortisone is available and is sometimes used in hospital settings in case of a critical condition. However, it inhibits the cortisol production of the adrenal gland, which can cause severe side effects. So this is not suitable for general application.

Intravenous procaine and lidocaine can also cause cardiac arrhythmia and neurological deficits. In critical clinical circumstances, these substances are sometimes administered by infusion.

All there is left for self-medication in case of corona contamination is pentoxifylline, 400 mg 2-3x/day, quinine or, on prescription, quinidine or chloroquine. Those who have been prescribed metamizole (in tablets or capsules) abroad have another option: In addition to an inhibiting effect on the synthesis of prostaglandins, metamizole has a relaxing effect on muscle tension. This is why the drug was often used to treat renal and gallstone colic and intestinal cramps in the Netherlands in the 1980s. It also provides relief in cases of common cold: it stops nasal discharge and opens the nasal cavities. As little as 1 mg suffices to obtain this effect (a normal tablet or capsule contains 500 mg!). The effect of such a small dose lasts approximately one hour; the effect of a 10-mg dose lasts three hours. The dosage of 1-2 tablets of metamizole 500 mg 3x/day, as recommended by the manufacturer, is dangerously high! This risk is discussed at length in an article by this author (15). A dose of 10 mg is far below the toxic threshold. A 50-fold dilution would result in capsules of 10 mg each. According to the manufacturer, adults can take 3x 50 of these capsules a day, which is far more than necessary. A common cold that has just started will determine the effective dosage by itself: after taking 1 capsule of 10 mg, the nose will stop running after approx. 30 minutes and will remain open for the next 1 to 2 hours, sometimes longer. When the symptoms recur, the patient can take the next table, etc. Usually, 4 to 5 capsules a day will be enough.
There is an easy way to dilute the drug: every chemist is able and allowed to do this. The patient hands in 1 or 2 tablets or capsules of the metamizole prescribed abroad and will receive 50 or 100 capsules of 10 mg in return. This will cost some money - the chemist can tell you how much - and will not be covered by any health insurance. The patient must be aware of the fact that the use of metamizole is strongly advised against in the Netherlands. This is explained in the article (15).

These capsules can be used in addition to 400 mg pentoxifylline 2-3x/day. Pentoxifylline may slightly reduce the blood glucose level and blood pressure. A preparation of quinine can be added.
This is a useful, more or less safe approach.

But it is not an approach that is supported in the Netherlands or that a reader of this article should apply without medical supervision. The author cannot estimate the risks for individual patients. A medical BIG-registered professional is competent to discuss this vision and approach with the patient.

Modern drugs, such as virus inhibitors, are being tested at several levels, but they are not easily available and their side effects are not all known yet. Moreover, they are much more expensive. Noticeable, based on long-standing literature, there seems to be a simple and available intervention to combat coronavirus. Of course, such interventions should not be experimented with without close supervision of a medical professional. There is not enough scientific evidence that this intervention is or will be effective in case of coronavirus. But in view of the nature of the medication, what we know about the substance and its side effects, it could be an alternative to doing nothing. In cases of mild symptoms of corona it is probably best to let the disease run its course, but in severe cases this medication could be a solution.

My old, long deceased professor's remark could be relevant for patients with very severe symptoms of coronavirus disease who need to be hospitalised: first administer an injection of calcium followed by an injection of euphylline (or pentoxifylline). This in combination with an injection of metamizole (7,8,9), as was the common post-operative practice at Erasmus University Rotterdam, could possibly save lives. In order to also improve the airway symptoms, it could be useful to add pentoxifylline. And to inhibit the virus production itself, a virus synthesis inhibitor should be administered as well.

Back to the title: how does this relate to pain management?

Similar processes play a role in the management of chronic pain, of which CRPS (Complex Regional Pain Syndrome) is a dramatic example. Similar dilemmas of treatment apply as described above and with the same type of drugs. The only difference is that there is no virus and no virus inhibitor. So, it is not surprising that a person who has dealt intensively with chronic pain for many years notices these striking parallels and similarity of dilemmas. It does not imply that chronic pain is a viral infection, but there are indications that a chronic inflammation (either sterile or non-sterile) plays a role in the chronic pain syndrome.

Hence these considerations on this page.

Written in private capacity.
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