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PRACTICES AND CONCEPTS

Hydroxy-chloroquine to treat COVID-19 – infected patients: Some lessons from medical anthropology and history of medicine



L'hydroxy-chloroquine pour traiter les patients infectés de la COVID-19 : quelques leçons d'anthropologie médicale et d'histoire de la médecine

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Summary It is certainly too early to take stock of Professor Raoult's intuitions, and moreover, that is not the aim of this short article. Nevertheless, experience has shown that in times of unprecedented health crises, prescriptions often turn out to be adventurous, especially when it comes to a new virus. The collective imagination around a remedy often takes the place of a guarantee or, on the contrary, a safeguard. Here, the authors question the implementation of hydroxy-chloroquine treatment in the context of the COVID-19 pandemic. How was his prescription discussed in this context of crisis? What lesson can we learn from medical anthropology and the history of medicine, by witnessing other epidemics and atypical or unconventional substances or behaviors of practitioners?

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Résumé Il est certainement trop tôt pour faire le point sur les intuitions du professeur Raoult, et ce n'est d'ailleurs pas le but de ce court article. Néanmoins, l'expérience a montré qu'en période de crise sanitaire sans précédent, les prescriptions se révèlent souvent aventureuses, surtout lorsqu'il s'agit d'un nouveau virus. L'imagination collective autour d'un remède se substitue souvent à une garantie ou, au contraire, à une sauvegarde. Ici, les auteurs s'interrogent sur la mise en œuvre du traitement à l'hydroxy-chloroquine dans le contexte de la pandémie de la COVID-19. Comment sa prescription a-t-elle été discutée dans ce contexte de crise ? Quelle leçon pouvons-nous tirer de l'anthropologie médicale et de l'histoire de la médecine, en étant témoins d'autres épidémies et de substances ou comportements atypiques ou non conventionnels des praticiens ?

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Introduction

When faced with a ward full of very sick patients with oxygen saturations in the low 1960s dying from a novel virus with no known therapy, what do you do? As Hippocrates taught; "For extreme diseases, extreme methods of cure, as to restriction, are most suitable" [1].

The antimalarial drug chloroquine and its safer derivative hydroxy-chloroquine ($C_{18}H_{26}ClN_3O$) have been used since the 1940s to treat chronic inflammatory diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren syndrome [2]. Chloroquine and hydroxy-chloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immuno-modulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells [3–6]. The use of chloroquine and of hydroxy-chloroquine-related compounds in the treatment of COVID-19 infection and post-infection has not come out of the blue [7] but goes back to the 2002–2003 SARS epidemic in Asia. This treatment showed antiviral activity (in vitro) against SARS coronavirus [8]. Recently chloroquine [9] and hydroxyl-chloroquine [10] have also been found to have

antiviral effects on COVID-19 in vitro, including inhibition of the viral entry and post-entry stages of infection.

So far, there are very limited data from controlled human trials of hydroxyl-chloroquine treatment for SARS-1 or COVID-19. Gautret et al. [11] treated 26 patients infected with SARS-CoV-2 with hydroxy-chloroquine and showed a decreased viral load in nasopharyngeal swabs; however, this study was limited by the small patient numbers and high dropout rate.

The physician: alone against the rest of the world

The COVID-19 pandemic put the Frenchman Didier Raoult on the front page of all Western journals. Since the start of the epidemics and then the pandemic, Professor Raoult has been in favour of using a drug combination (hydroxy-chloroquine + azithromycin) that shows a good in vitro antiviral effect against COVID-19 but without "robust" human clinical trials behind it [12,13]. Trials have not been carried out according to the current standards of biomedical research with a double-blind randomised controlled design. Consequently, he is criticised by physicians and

scientists from many countries, starting in France because of his unorthodox approach and thinking. Despite this criticism it is now in national guidelines for the management of COVID-19 patients in Italy [14,15], Spain [16], and also the United States [17].

Let us be clear, the question is not to take a position for or against Professor Raoult; history and further biomedical publications will tell us later whether he was right or not. The purpose of this short article is to show what the history of medicine can bring to the question, and how it tells us about taking shortcuts with therapeutic innovation during a major crisis.

How can the history of medicine inform us in this controversy, especially during a novel death-dealing pandemic? Many discoveries over time have been made by people who are not part of the establishment e.g. James Lind (1716–1794), a British naval surgeon from Edinburgh, now considered the founder of EBM, carried out one of the first controlled clinical trials recorded in medical science, demonstrating that oranges and lemons could treat scurvy, but many years had to pass before the Royal Navy introduced them in the sailors' diet [18], the circulation of the blood (William Harvey, in the *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, 1628), strongly refuted at the time by Jean Riolan and Guy Patin, the dry treatment of the wounds with gauze and clean dressings (Robert Wood Johnson, American pharmacist), the use of medical percussion (Leopold Aenbrugger, Austrian physician and music composer), the discovery of *Helicobacter pylori* as the cause of gastrointestinal ulcer (Barry Marshall). In orthopaedics in the UK, for many years, no major advances came out of university departments or teaching hospitals; artificial joints were developed by surgeons in district hospitals Charnley in Wroughton, McKee in Norwich, Ring in Redhill, and Ling in Exeter. McKee made his prototype hip replacements in his garden shed in the 1950s. Major advances are often made by people who are not main stream. Sterling Edwards, a pioneer in cardiovascular surgery kept cow hearts in his fridge at home to use when developing artificial grafts and valves. Then there is the Hungarian obstetrician Ignaz Semmelweis (1818–1865), initiator of hand-washing following autopsies of obstetric patients to limit the risk of puerperal infection. He was mocked, criticised and hated, causing mental distress before subsequently being rehabilitated [19].

What "miracle" molecules in times of crisis?

It is obvious that certain drugs, currently frequently used, would never be put on the market today if they passed modern quality controls, and yet, we could not do without them. Examples are paracetamol, aspirin, sulphamides (derived from aniline, a popular dye), and even hydroxy-chloroquine (because of the heart decompensation risk). Unfortunately some deaths of patients infected with COVID-19 have been reported to be due to misuse of hydroxy-chloroquine, or even chloroquine (although this drug is not part of the therapeutic arsenal proposed). Some patients had self-medicated, or cardiac contraindications had not been taken into account, causing paroxysmal rhythm disturbances and

sudden deaths [20]. These complications are reminiscent of those observed during the Spanish flu (pandemic of 1918), where many deaths in the United States (at least 3%) were attributed, not to the direct action of the virus, but to an overdose of aspirin; official dosage recommendations are clearly excessive [21].

Amantadine was originally introduced as an antiviral drug to treat influenza A. Some patients noticed relief in their Parkinson disease symptoms after taking amantadine for influenza. This clinical observation sparked an initial interest, and promoted several important studies that eventually led to a new indication of this drug. Interestingly amantadine is discarded as influenza medication nowadays for lack of efficacy [22].

The literary figure of the madman or the enlightened one

Shakespeare is worth reading again, since COVID-19 can be considered our plague [23]. In *King Lear*, the tragedian teaches us that the truth sometimes comes from the mouths of the Fool, the only character in the play to speak with sincerity to the sovereign, without twisted speech, but with coldness and righteousness.

For many clinicians, when facing a similar emergency with a great number of deaths, history has showed to us that it may be ethically and legally correct to act without confirmed robust clinical trials. Anything is worth trying to save even a low number of human lives and bringing some hope to mankind; at least as long as trials disproved positive therapeutic effects or a more efficient therapy is available.

Returning to the discussion on hydroxy-chloroquine the look into the history of medicine offers one strong argument for the application as a potential treatment due to the lack of proven effective therapies for COVID-19 [3].

The second argument comes from already existing observations on hydroxyl-chloroquine from in vitro experiments and clinical observations from previous other viral infections. Currently, resuscitation services are overwhelmed in many countries; containment procedures have only a partial effect in reducing the incidence of the disease, but without preventing its spread or the congestion of hospital services. If at the pandemic's start, the main goal was to avoid the saturation of the intensive care units, now the main goal is to reduce the number of patients developing severe acute respiratory syndrome. So it needs to plan a treatment in early stage of disease. It is to save time, but not to eradicate the disease, especially since the second wave of the pandemic has begun in Asia, and will soon hit Europe again, and the rest of the world; as has been shown in the evolution of the ancient epidemics in the past (plague, yellow fever, cholera).

Conclusion

Other comparisons would have been possible (one thinks of the introduction into clinical practice of "discussed" molecules such as cinchona, antimony, or arsphenamine), other authors could have been called upon in medical anthropology (like Byron J. Good, from Harvard Medical

School, and his work in the field of professional and individual acceptance and dissemination of treatment for mental illness), but this article is intended as a first approach, a first look, a strong introduction.

So certainly, in the context of hydroxy-chloroquine and COVID-19 pandemic, there are rules to follow, those of statistics and randomised controlled trials, but do we have the time? This is the key point – the major question. We just ask the question. History has the answer.

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N/A.

Patient consent

N/A.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

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