EDITORIAL

SMELL DISORDERS CAUSED BY COVID19 EMERGING TREATMENT A STUDY CASE–CONTROL FOR SMELL DISORDERS POST COVID19

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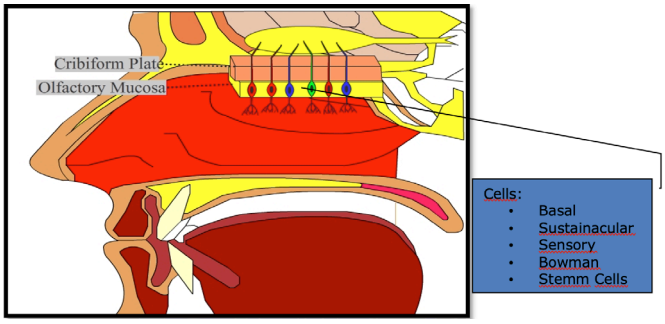
ABSTRACT

Chronic olfactory disorders have been reported in many COVID-19 patients. Only in the U.S., ca. 1 million people may be affected (Khan 2022). SARS-CoV-2 viral particle persistence, and associated inflammation in the olfactory neuroepithelium, may account for prolonged or relapsing symptoms of COVID-19, such as persistent smell loss (Dias de Melo 2021) (1).

Keywords: covid19, Olfactory disorders, Fusimed B, fusidic acid, betametasona.

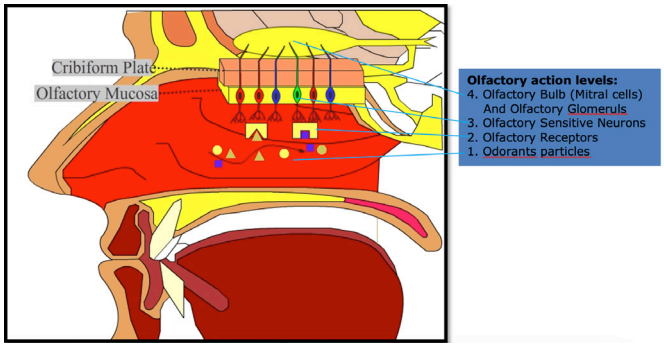
INTRODUCTION

THE OLFACTORY EPITHELIUM (O.E.). The O.E. has five types of cells: basal, sustainacular, sensory, Bowman (secretory glandular cells) and Stem cells that regenerate the epithelium every 6 to 8 weeks (almost complete turnover in cellular material)(8) Picture1.



Picture 1: Olfactory Epithelium, Cribiform plate and Olfactory mucosa with five type of cells

Odorants bind to specific olfactory receptors at the olfactory epithelium stimulating dendrites of olfactory-sensitive neurons, their axons reaching the mitral cells in the olfactory bulb. Picture 2



Picture 2: Olfactory action Levels: 1: Odorante particles 2: Olfactory Receptors 3: Olfactory Sensitiv Neurons 4: Olfactory glomeruls 5: Olfactory bulb (Mitral cells).

Treatments tested as nasal and oral corticosteroids, thioctic acid, B vitamin complex, were not effective in most patients.

Only a small percentage improved, which could correspond to those who heal on their own regardless of any treatment.

In September 2021, there was the fortuitous observation of a case of severe hyposmia of 16 months of evolution after COVID19, which was treated with Fusimed B® for another diagnosis (epistaxis due to acute rhinitis), with complete smell recovery in the span of two weeks.

We developed a protocol for the use of Fusimed B® in the treatment of post-Covid19 smell disorders, to evaluate its effectiveness. (Loiacono F.L.)(6)

The Preliminary communication was made on 12/08/2021. This Protocol was efficient in most of the cases (87%) in which it was administered.

MATERIAL Y METODOS

We studied two groups of patients with olfactory disorders post COVID19.

a) cases, and b) controls

Both groups were evaluated to certify that they had COVID19 by rapid test and PCR and also were evaluated for olfactory disorders by periodic smell testing (coffee, chocolate, mint, lemon, cloves). Results were recorded before treatment and 8 weeks after treatment.

All patients suffered from hyposmia, anosmia and 25% of them, suffered dysosmia.

The statistical evaluation seeks to validate the Hypothesis that treatment with Fusimed B in patients with post-COVID19 olfactory disorders was statistically significant.

Inclusion criteria:

- Anosmia, hyposmia, dysosmia, parosmia Post Covid19 (exclusive)
- Normal smell before Covid19 (exclusive)
- Absence of sinonasal polyposis that reduce or blocks nasal airflow
- Adherence. to treatment
- Not having allergies to the components of the medication to be indicated
- Absence of intolerances that do not allow .compliance with the scheme
- Consent to the application of the treatment in writing Form.
- Telephone follow-up weekly (WhatsApp)

Exclusion criteria:

- Anosmia, hyposmia, dysosmia, parosmia not related to Covid19 (exclusive)
- Lack of .adherence to treatment
- Presence of intolerances (nausea -1 case-, rejection due to smell/taste -1 case-)
- Allergy to the components of the indicated medication
- Presence of sinonasal polyposis that reduce or blocks nasal airflow
- Not consenting the treatment in writing Form
- Impossibility of Telephone Tracking (WhatsApp)

Treatment had three steps as follows

1° of 3) Exclusion of Volatile Compounds from their Environment

All patients were instructed to avoid volatile compounds that alter the functioning of the respiratory mucosa. We gave them this written instruction:

Avoid environments with these products:

- Bleach, CHLORINE (INCLUDING POOLS), AMMONIA,
- Household sprays
- SAHUMERIOS, PALO SANTO, Smokes in general
- Air freshener, STOVE, Aspirate of alcohol
- SOLVENTS (Thinner, Turpentine, Naphtha, Acetone)

2° of 3) Restoration of nasal patency if necessary

In patients with reduced passage of air through the nostrils induced by rhinitis, we indicated corticosteroid sprays (fluticasone) and oxymetazoline for a week prior to Treatment, to facilitate the progression of the Fusimed B ® emulsion (the treatment itself).

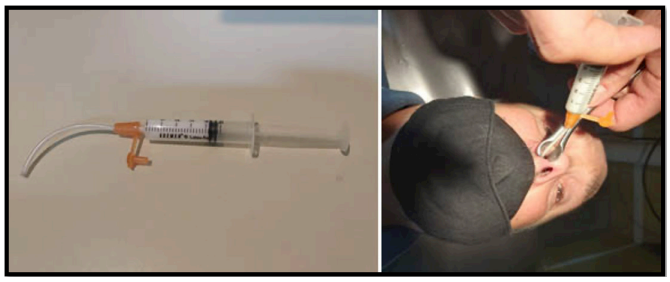
3º of 3) The treatment itself was started:

- I.N.D.A -Intra Nasal Directed Application- of Fusimed B®

and then:

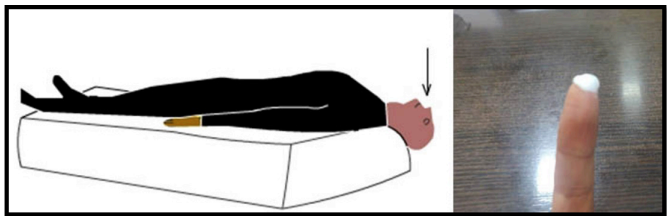
- Patient Self-application of Fusimed B® up to 8 weeks.

I.N.D.A. IntraNasal Directed Application: I used a Syringe with a dose of 2.5 c.c. of Fusimed B®, with 6 cm long catheter –type K30- with blunt distal end to avoid injuries in the cribiform plate. INDA was performed only once at the start of treatment, Picture 3.



Picture 3: syringe and 6 cm catheter with blunt distal end, and Application directed towards the cribriform plate

Patient SELF-APPLICATION: Patient Self application of 0.5 c.c. of Fusimed B® at their home (Picture 5) , in Ross position (Picture 6), every 8 hours for 2 weeks, and every 12 hours from the 3rd. until the 8th week if necessary. Picture 4.



Picture 4: Ross Position to Fusimed B® auto application and amount of Fusimed B® applied at each opportunity

Fusimed B® Formulation:

Fusidic Acid 2% + Betamethasone 0.1%. (Excipients: Vitamin E, Butylhydroxytoluene, Ceramide, self-emulsifying wax, Edetate disodium, Sodium hyaluronate, Isopropyl myristate, Xanthan gum, liquid petroleum jelly, purified water).

Emulsion = It has a more aqueous content in its formula, which allows greater diffusibility

Producer Laboratory = Pablo Cassará S.R.L. Laboratory. Carhué 1096 – La Rosa s/n between Avenida Gral. Paz and Saladillo, Autonomous City of Buenos Aires. Argentinian Republic.

TOTAL Amount of BETAMETHASONE Applied: I.N.D.A. + Self-application for 8 weeks = 16.8 g.

TOTAL PATIENTS (to whom Fusimed B® was indicated) = 39

EXCLUDED (*) = 16 (WOMEN = 8 :: MEN =8)

Patients who participated in the protocol 39 –16 = 23

(*) Reasons for exclusion:

- DID NOT DO THE TREATMENT
- Did the treatment partially
- One patient didn't TOLERATE the treatment (nausea)
- Patients that did not understand the instructions (hourly frequency, quantity, application mode)
- Poor communication between doctor and patient (by WhatsApp).

DISTRIBUTION OF CASES AND CONTROLS BY AGE AND SEX

Casos (23) Grupos por Edad y Sexo	Hombres	Mujeres
< 20 años	2	0
20 a 30 años	0	2
31 a 40 años	1	6
41 a 50 años	1	4
51 a 60 años	0	4
> 60 años	1	2
TOTAL (23 casos)	5	18

Controles (28) Grupos por Edad y Sexo	Hombres	Mujeres
< 20 años	1	2
20 a 30 años	2	8
31 a 40 años	2	3
41 a 50 años	0	2
51 a 60 años	2	2
> 60 años	2	2
TOTAL (28 controles)	9	19

Table1: Cases and controls by Age and Sex

RESULTS

TOTAL of CASES (who did the treatment correctly)

	Recovered	Not recovered	Total
Female	15	3	18
Male	5	0	5
Total	20 (87 %)	3 (13 %)	23 cases

Table 2: There was no significant difference in the response rate related to gender. P= NS (not significant :: chi square test)

Table of Controls: (Those who did not receive the treatment)

- 20% of Patients with olfactory disorders treated with Fusimed B®, recovered their smell sense after two weeks of treatment.
- The remaining 80% needed to extend the treatment up to 8 weeks.
- Among those who did not obtain improvement after the 8th week, an extension of the treatment was tried in a small group, without results. Tabla 3.

	Recovered	Not Recovered	Total	Value of p
Cases	**20 (87,0%)**	3 (13,1%)	23	p < 0,0001 chi square test
Controls	**5 (17,9%)**	23 (82,1%)	28	

Table 3: Results Comparision between Cases and Controls

- 20% of Patients with olfactory disorders treated with Fusimed B®, recovered their smell sense after two weeks of treatment.
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Among those who did not obtain improvement after the 8th week, an extension of the treatment was tried in a small group, without results.

Recovery of CASES (Who did the treatment)

Total 23 (Female 18 :: Male 5)

Recovered = 20

- 4 recovered within first two weeks = 20%
- 16 recovered between 3rd. and 8th. week = 80%

DISCUSSION

The results in this protocol showed efficacy in 87% of the cases in which the treatment was administered.

It could be the action of Fusidic acid plus Betamethasone on the olfactory epithelium that caused relief or cure of olfactory disorders.

The action was probably enhanced by the emulsion vehicle used, which allowed the active ingredients to persist for a longer time on the nasal mucosa.

Fusidic acid activity (FAA) has demonstrated to be useful against staphylococcus aureus.

Initially, anosmias/hyposmias characterized the olfactory disorder of COVID19.

These symptoms were used to suspect the disease, in association with flu-like symptoms but also, as the only manifestation.

It has been reported the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in respiratory cultures in

patients hospitalized with COVID-19 pneumonia(3).
The inflammation generated by Staphylococcus aureus has been demonstrated through the release of proinflammatory peptides such as enterotoxin B, inducing inflammation mediated by proinflammatory cytokines(4).
Fusidic acid activity (FAA) was evaluated against 2.002 clinical staphylococcal isolates collected in U.S. Hospitals inhibited 99.8% of Staphylococcus aureus isolates. In conclusion, FAA demonstrated sustained, potent activity against this recent collection of U.S. staphylococci. (5)
The global emergence of methicillin-resistant Staphilococcus Aureus (MRSA) and strains with reduced Vancomycin susceptibility have limited treatment options.
For orally available antistaphylococcal agents, surveillance in the United States in 2013 found fluoroquinolone (levofloxacin), erythromycin and clindamycin resistance rates of 64.2%, 87.8%, and 26.7%, respectively, among MRSA isolates, with an overall prevalence of 47.9% (5)
SARS-CoV-2 is transmitted through the human nasal mucosa via the angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), which are highly expressed in the nasal epithelium.
Both ACE2 and TMPRSS2 transcriptions significantly decreased in nasal epithelium in response to S. epidermidis and were relatively lower in human nasal mucus with large numbers of S. epidermidis.
Olfactory disorders in the COVID19 pandemic had clinically four stages.
Olfactory Disorders began in March 2020 (Ushuaia, Argentina), strongly increasing their incidence and prevalence by September 2020, with periodic outbreaks.
This occurrence continued during 2021, to decrease and almost disappear with the presence of Omicron.
4 Stages can be distinguished regarding Olfactory disorders from the start of the pandemic at the beginning of 2020 until August 2022, when the present analysis was completed.(*)

STAGE 1. We can distinguish two groups of patients:
• *Group A:* 80% of all patients with smell disorders, cured without treatment within the first two weeks
• *Group B:* The remaining 20% didn't resolve the symptoms, despite the indicated treatments (B vitamins, Thioctic acid, nasal corticosteroid spray and olfactory retraining).

STAGE 2. As the months passed, some recovered patients from Group A lost their sense of smell again.
In some of the recurrences, reinfection by SarsCov2 was diagnosed. In others it couldn't be confirmed due to operational difficulties in carrying out massive tests.
In most of these cases the smell disorders becoming chronic.
(*) it happened in Ushuaia, Argentina

STAGE 3. A smaller percentage of patients with relapses developed Dysosmias. Two types of dysosmias were identified:
• *Uniform dysosmias:* was the most frequent. The patients were able to smell, but most of the time they felt the same odor for different odorants.
The rest of the odorants were either not perceived or perceived normally.
• *Parosmias:* the smell perceived of some odorants was unpleasant (rotten smell or similar). Some patients refused to eat and even didn't share the table with their relatives.

Uniform Phantosmias, there were Patients who smelled an aroma that did not exist in the environment, but like Uniform Dysosmias, they always perceived the same aroma.
Parosmic Phantosmias, In these few cases, the patient always perceived the same non-existent unpleasant aroma.

STAGE 4. Stage 4 was established towards the end of 2021 and during the year 2022 (until August when these observations are written).
This stage is contemporaneous with the application of vaccines (SPUTNIK I AND II, COVISHIELD, SINOPHARM, AZTRA ZENECA, PFIZER, MODERNA, CONVIDECIA, COMINARTY -PFIZER BioNtech- *) and the appearance of Omicron.
In stage 4 smell disorders decreased in incidence with few new cases.
Only the prevalent cases remained.
Hyposmias and anosmias continue appearing with rapid recovery in a few days, as the initial manifestations of flu-like symptoms as occur with influenza.

* Source: Ministry of Health (Argentina), list of vaccines available for application
https://www.argentina.gob.ar/coronavirus/vacuna/cuales

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CONFLICT OF INTERESTS

The work was carried out freely without any conditioning, from the discovery of the treatment to the present.

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