Journal of Clinical Pediatrics Research

Bittmann S, 2022- J Clin Ped Res
Correspondence

A Present Update of Camostate and the Role in SARS-CoV-2 Infection

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Received Date: 05-14-2022

Accepted Date: 05-19-2022

Published Date: 06-15-2022

Keywords: SARS-CoV2; S-protein; Camostate; Protease.

SARS-CoV-2 has triggered a pandemic of "coronavirus disease-2019" (Covid-19). Viral cell entry of coronaviruses relies on the binding of viral spike protein (S protein) to cellular receptors and S type of protein processing by the host cell proteases. It is known that SARS-CoV-2 uses the human receptor ACE2 for cell entry and the serine protease TMPRSS2 for "priming" of the S protein. Camostate has antiviral properties against coronaviruses. The effects are due to inhibition of the endogenous protease TMPRSS2, which the SARS-CoV-2 virus requires for the host cell entry (as well as exit). Camostate is a serine protease inhibitor. Camostate, which is already in clinical use, reduces cell infection. So far, this has been shown exclusively in cell lines or cell cultures, which do not reflect the complexity of the three-dimensional alveolar lung cell association with type I, type II cells, endothelial cells and alveolar macrophages. It is well known, that Camostate blocks TMPRSS2 and related proteases [1-36]. For SARS-CoV-2 to enter lung cells, the virus must be activated by the cellular protease TMPRSS2. Camostate is used in Japan to treat inflammation of the pancreas, blocks the protease TMPRSS2 and thereby inhibit SARS-CoV-2[1-18,20-29,31-35]. However, it was unclear whether the camostate degradation product GBPA also inhibits the virus and whether the virus can use related proteases for infection in addition to TMPRSS2, which may not be inhibited by camostate [18,20,29]. These proteases are available to the virus for replication in the upper respiratory tract and are inhibited by camostate [1-36]. It is therefore not possible for SARS-CoV-2 to evade the antiviral effect of Camostate by switching to related proteases instead of TMPRSS2. In further studies, the researchers were able to show that in addition to Camostate, the primary Cam state metabolite GBPA also inhibits the protease TMPRSS2, thereby blocking SARS-

Citation: Bittmann S. A Present Update of Camostat and the Role in SARS-CoV-2 Infection. J Clin Ped Res. 2022;1(1):15-19.
DOI: https://doi.org/10.37191/Mapsci-JCPR-1(1)-005

CoV-2 infection. Camostate is converted to GBPA in the body within a very short time. GBPA can exert an antiviral effect in patients. A higher dosage of Camostate to effectively treat COVID-19 than to treat pancreatic inflammation may be required [33,36]. Inhibition of SARS-CoV-2 by Camostate had initially been shown only in the lung cell line Calu-3 [6]. The involvement of researchers from Hannover, Germany, made it possible to analyze the antiviral effect of Camostate in real lung tissue as well [6]. Camostate and GBPA inhibit SARS-CoV-2 infection of lung tissue [15]. The camostate mesilate-containing drug Foipan® has been available on the Japanese market since 1986 [1-36]. It is used to treat chronic inflammation of the pancreas and postoperative reflux esophagitis [33,36]. According to the product information, the substance has an inhibitory effect on several enzymes and intervenes in various systems in the body. Among other things, an inhibitory effect on trypsin and normalization of amylase levels are mentioned [33,36]. However, the reason why this substance suddenly becomes interesting in the corona crisis is different [24,26,30].

Camostate is defined as 4-[[4-[(Aminoiminomethyl)amino]benzoyl]oxy]benzen-essigsäure 2-(Dimethylamino)-2-oxoethylester-methansulfonat; FOY 305; FOY-S 980; Foipan -mesylat) [1-36]. The empirical formula is $C_{20}H_{22}N_4O_5.CH_3S=_3H$ [24,35]. The molecular weight is 494.52. The melting point is between 164-168 degrees. Camostate is stored in the refrigerator. The UN No. is 3077, the CAS No. is 59721-29-8. Camostate belongs to the protease inhibitor class of drugs, and its mechanism of action is antifibrinolysis [1-36]. Camostate is a synthetically produced active ingredient from the protease inhibitor group [1-36]. It is approved in Japan as Foipan (manufacturer: Ono Pharmaceutical) for the oral treatment of chronic pancreatitis and postoperative esophagitis caused by reflux of gastric acid [33,36]. Chemically, camostate is a derivative of p-aminobenzoic acid. The active ingredient is used medicinally as camostate mesilate, i.e., as the salt of methanesulfonic acid [1-36]. Camostate inhibits in vitro various pancreatic and plasmatic proteolytic enzymes such as trypsin, plasmin, pancreatic kallikrein, plasma kallikrein, and thrombin, as well as the hydrolytic activity of C1r and C1 esterase [33,36]. Camostate further inhibits the cellular protease TMPRSS2 in vitro [1-18,20-29,31-32,34,35]. The efficacy of Camostate in different cell cultures has already been demonstrated [1-36]. Camostates inhibits TMPRSS2, the enzyme is expressed on the human cell surface after autocatalytic activation, mainly in the small intestine and to a lesser extent in the liver, heart, prostate, thymus and lung [1-36]. As per the analysis, SARS-CoV-2, virus responsible for the COVID-19, requires TMPRSS2 exists in human body to get inside the host cell, which may provide target for the treatment [1-18,20-29,31,32,34,35]. Therapeutic efficacy in COVID-19 patients remains to be tested in clinical trials [2-4,6,24,32]. Similarly, it is to be investigated whether active elements can be injected directly to the lungs. It is unclear whether camostate per se is sufficiently available in the lungs. According to scientific information of the German Federal Institute for Drugs and Medical Devices, the necessary doses, extrapolated from results obtained in cell cultures, would be so strong in patients of standard weight that serious side effects could occur. Camostate is among drugs for which the German Federal Ministry of Health started the central appropriation in April 2020 for the treatment of the

infection along with severely ill cases of COVID-19 patients in Germany. Since the COVID-19 therapy an individual therapeutic trial without any clinical evidence of virtue, its usage must be implemented on the patient-by-patient basis, primarily for severe forms of the disease.

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