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REVIEW ON: A MECHANISM ACTION OF FAVIPIRAVIR(T-705) AGAINST TARGETAL VIRAL RNA POLYMERASE

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ABSTRACT

Favipiravir is a pyrazine carboxamide derivative (6-fluoro-3-hydroxypyrazine-2-carboxamide) and a broad-spectrum antiviral drug approved by the Drug Controller General of India (DCGI) an antiviral drug commonly used for treating influenza for the treatment of mild to moderate cases of COVID-19 in India. Favipiravir is a prodrug that is metabolized in cell to active form favipiravir-ribosyl triphosphate (favipiravir RTP). When drug enters it gets mostly metabolized by aldehyde oxidase (AO) which it forms inactive metabolite(T-705M1) and partly hydroxylate form by xanthine oxidase (XO), further favipiravir RTP active form which binds to RNA dependent RNA polymerase (RdRp) and inhibit the viral replication. Here we discuss about mechanism of action of favipiravir to targeted viral RNA polymerase as well as their adverse effect to other body organs.

KEYWORD: Favipiravir, Mechanism of action, Adverse effect.

INTRODUCTION

Favipiravir (Trade name: Avigan) is a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazinecarboxamide, T-705) and broad-spectrum antiviral drug was discovered against the influenza virus by Toyama Chemical Co., Ltd in japan, 2014.[1] Recently, Wang et al experiment that favipiravir was effective in decreasing the SARS-CoV-2 infection. Lately, it was authorized by the National Medical Products Administration of China (NMPA) as the 1st anti-Covid-19 drug in China, with negligible adverse effects.[2] After that, it also permitted by the Drug Controller General of India (DCGI) an antiviral drug generally used for treating infection – for the treatment of mild to moderate cases of Covid-19 in India. Before it was used in Ebola, Nipah, zika virus disease cases.[3] Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase, and effective against all subtypes and strains of influenza viruses including ones resistant to promoted neuraminidase and M2 inhibitors. Favipiravir demonstrated anti-viral activities against other RNA viruses, on the other hand it shows high risk for teratogenicity and embryotoxicity. So, the Ministry of Health, Labor and Welfare decided conditional marketing sanction with strict regulations for its manufacture and clinical use.[4] It function as purine analogue and is incorporated instead of guanine and adenine. Favipiravir half maximal effective concentration (EC_{50}) = 61.88 μM required to reduce the SARS-CoV-2 infection.[5]

1. Mechanism of Action: Favipiravir is a prodrug that is metabolized in cell by phosphoribosylation to active form favipiravir-ribosyl triphosphate form (favipiravir RTP), which selectively binds to replication site and prevents the RNA-dependent RNA polymerase (RdRp) and avoiding viral transcription and replication are represent in Fig. 1.[6]

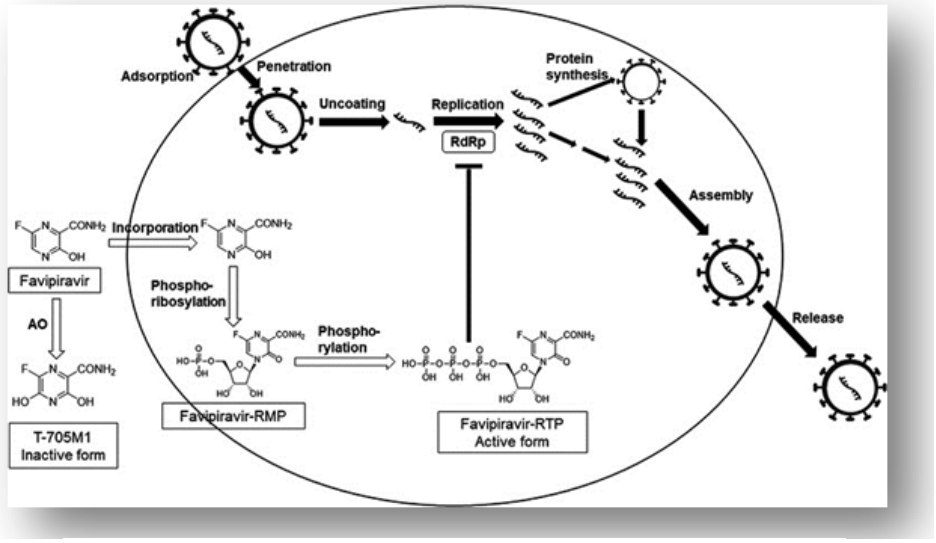

Fig 1: Mechanism action of favipiravir to inhibiting viral replication.

1.1 Pharmacokinetics of favipiravir: Favipiravir is member of pyrazine and primary carboxamide. The parent drug orally administers, when enters the body it gets metabolism in the liver mainly by aldehyde oxidase (AO), and partially hydroxylated by xanthine oxidase, producing an inactive oxidative metabolite T-705M1 and excreted by the kidneys.[7] Remaining moiety gets amalgamation enters to cell. Favipiravir undergoes two process i.e. phosphoribosylation and phosphorylation. In phosphoribosylation addition of single moiety of ribofuransyl into favipiravir, which get amend into favipiravir-ribofuranosyl-50-monophosphate (RMP).[8] After that under phosphorylation, addition of two phosphate group and metabolized via intracellular enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) to generates favipiravir-ribofuransyl-5'-triphosphate (RTP) in active form and this active form gets react with Rdrp and pause the further cycle of transcription of chain as well as replication of virion, which are represent in Fig.2.[9]

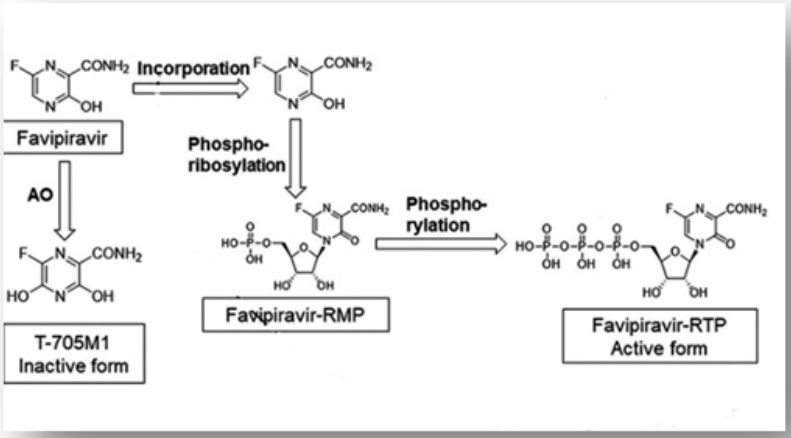

Fig 2: Drug incorporation while entering into cell.

1.2 Favipiravir interact to virion: At entry of virion into host cell it gets transcript or replicate with the help of host nucleus DNA sequence on ORF1a and ORF1b segment in SARS-CoV-2.[10] The dose of favipiravir which have favipiravir-RTP binding pocket which binds to in between ORF1a and ORF1b, inhibit the action of genomic replication, sub genomic replication of nucleocapsid, spike, membrane, envelope protein which represent in Fig.3.[11]

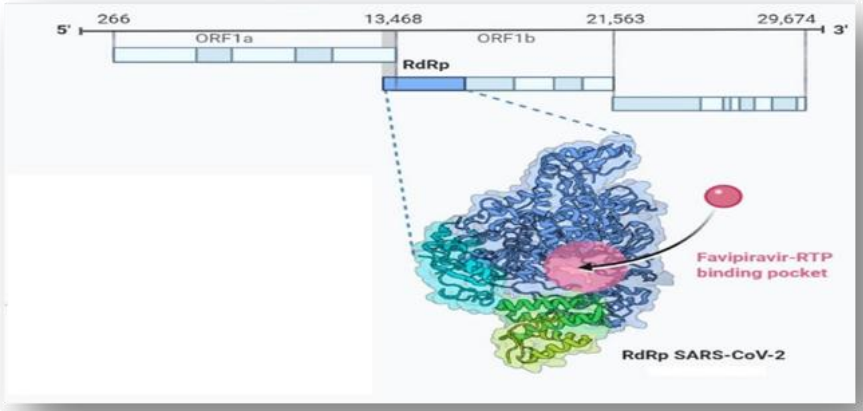

Fig 3: Favipiravir-RTP binding to replication site.

The posology of favipiravir to Covid-19 patient gives to tablet on 1st day 1800mg twice a daily and after that 800mg on ward twice a daily up to 14 days, as directed by physician. From studies the plasma protein binding of favipiravir was 54% in humans. The bound percentage of favipiravir to human serum albumin 65.0% and α-1 acid glycoprotein 6.5%. Favipiravir's apparent volume of distribution range from 15 to 20 Litre and is possible restricted to vascular and extra vascular fluids.[12] In vitro antiviral activity favipiravir effectively inhibits SARS-CoV-2 infection in Vero E6 cells half maximal cytotoxic concentration (EC_{50}) = 61.88 µmol/L, half maximal cytotoxic concentration (CC_{50}) > 400 µmol/L, selectivity index (SI) > 6.46.[13] The major drug interaction observe that inhibit irreversibly AO and inhibit CYP2C8 in dose dependent manner, there is no inhibitory activity of XO. But the hydroxylated metabolite shows weak inhibitory activity to CYP.[14] Favipiravir has low risk of drug interaction possible with use of theophylline and paracetamol. It may increase the concentrations of pioglitazone or repaglinide with affiliated use that primes to risk of hypoglycaemia.[15]

2. Adverse effect: In phase three clinical trials for the treatment of influenza, the adverse effects of favipiravir cause reduced in body weight, vomiting, gastrointestinal disturbance, reduced locomotive activity, reduced production of RBC, an increased liver function such as the production of aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, uric acid level and total albumin. Contraindication like women known or suspected to be pregnant or lactating women, severe hepatic impairment, severe renal impairment. As well as major undesirable effects observed in clinical studies is increase of blood uric acid level and diarrhoea.[16] Based on the study in trial animals, favipiravir shows teratogenicity and embryotoxicity. The usage of favipiravir is inadvisable in women who are pregnant. For females of gestation potential, the use of appropriate contraception is advised up to 7 days after the end of treatment. As well as men who have occupied favipiravir and have partners of gestation potential are advised to use condoms up to 7 days after the end of the treatment. The use of favipiravir in paediatrics is not suggested based on the results in juvenile animal toxicity studies.[17] In an in vitro study, favipiravir inhibits hERG current at a concentration of 157 µg/ml, which is three times sophisticated than maximum concentration reached in humans at a therapeutic dose. The risk of QT interval prolongation of favipiravir is considered to be not high. In normal people, the effects of single-dose 1200 mg and 2400mg of favipiravir on QT intervals did not vary from subjects getting placebo.[18]

CONCLUSION

From above study of favipiravir we concluded, it's best primary medical treatment for covid patient but, the from survey of government medical counsellor drug shows serval side effect so, it's risky to take and always before taking such types of medication you will need to counselling to your family doctor. There is no proper vaccines for Covid-19. So, it's an emergency medication to against the pandemic mild or moderate Covid-19 disease case.

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