ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI (AP)

PHARMACOLOGY BULLETIN

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FROM THE EDITORIAL DESK….

Welcome to the Fourth Issue of 'ESSENCE' from AIIMS Mangalagiri,

We are in the midst of the COVID 19 pandemic which has now affected more than 4 million people with approx 2.5 lakhs deaths till date. With increasing cases and fatalities there is a sense of urgency to identify drugs both old and new that may have beneficial effects on the disease morbidity and mortality. The current issue highlights the various issues involving the use of drugs that have been employed so far in the fight against COVID 19.

Disasters and pandemics like COVID 19 pose unique challenges to providing health care. In the scenarios of pandemics and disasters, sessions of telemedicine can reduce the risks to both health care workers and patients, and thus prevent the transmission of infectious diseases. Institutions invested in telemedicine help to increase the available human resource and allocate them at the respective hospitals to provide physical care for patients in the time of crisis like this. With Covid-19 cases spreading across the country, India formally recognised the practice of telemedicine recently. The government's new "telemedicine practice guidelines" legitimise the practice of remote consultations. The current issue discusses the guidelines pertaining to prescribing medications as per these new telemedicine guidelines.

Further, like always, the current issue also discusses the recent drug approvals and also safety alerts of various drugs. Finally, the readers can test their pharmacology knowledge with the cross word puzzle on 'Drugs causing Hyperkalemia '.

Happy Reading & Stay Safe.

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri (Andhra Pradesh) at email id: pharmacology@aiimsmangalagiri.edu.in

Role of various drugs and treatment modalities in COVID-19

a) HCQS and Chloroquine:

Chloroquine and hydroxychloroquine (HCQS) have a long-standing history in the prevention and treatment of malaria and other chronic inflammatory diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells. HCQS can change the acidity at the surface of the cell and hence can prevent the virus from infecting it.

Both Chloroquine and Hydroxychloroquine have shown in-vitro activity against SARS-CoV-2. There have been a few small studies which seem to suggest that these drugs lead to enhanced viral clearance, and reduced disease progression. A few studies have reported that the addition of Azithromycin to HCQS resulted in numerically superior viral clearance. However, the concerns of additive cardiotoxicity with combination therapy do not support adoption of this regimen without additional studies.

In the meanwhile, ICMR has recommended the use of HCQS for chemoprophylaxis in health care professionals and also in asymptomatic contacts of COVID positive cases. Currently, there are several RCTs of both chloroquine and hydroxychloroquine examining their role in COVID-19 treatment and the results of these studies are expected to generate the evidence on the efficacy of these drugs in COVID 19.

b) **Lopinavir/Ritonavir:**

Lopinavir/Ritonavir, is an approved oral combination for treating HIV, demonstrated in vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease. There have been some case reports of lopinavir/ritonavir for the treatment of COVID-19. The timing of administration during the early peak viral replication phase (initial 7-10 days) appears to be important because delayed therapy initiation with lopinavir/ritonavir had no effect on clinical outcomes. The most commonly used and studied lopinavir/ritonavir dosing regimen for COVID-19 treatment is 400 mg/100 mg twice daily for up to 14 days. Although additional RCTs of lopinavir/ritonavir are ongoing, the current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment.

c) Remdesivir:

Remdesivir is a prodrug that undergoes metabolism to an active C-ATP. The first clinical use of Remdesivir was for the treatment of Ebola; Currently, Remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent in vitro activity against several nCoVs, including SARS-CoV-2 where it can block the RNA dependent RNA polymerase (RdRp) of the virus. Clinical trials are ongoing to evaluate the safety and antiviral activity of remdesivir in patients with mild to moderate or severe COVID-19. Recently, the U.S. Food and Drug Administration issued an emergency use authorization for Remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. There are studies currently underway to generate more data on this.

d) Favipiravir:

Favipiravir inhibits the RNA polymerase, halting viral replication. Most of favipiravir's data are derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses. Limited clinical experience has been reported supporting the use of favipiravir for COVID-19. In India Glenmark is conducting a clinical trial to evaluate favipiravir in the treatment of COVID 19.

e) Convalescent Plasma Therapy:

Another potential adjunctive therapy that is being investigated for COVID-19 is the use of convalescent plasma or hyperimmune immunoglobulins. The rationale for this treatment is that antibodies from recovered patients may help with both free virus and infected cell immune clearance. In theory, the benefits of this therapy would accrue primarily within the first 7 to 10 days of infection, when viremia is at its peak and the primary immune response has not yet occurred. Anecdotal reports or protocols for convalescent plasma have been reported as salvage therapy in some cases of COVID 19. In India, ICMR has initiated a Phase II multi centric trial to evaluate the safety and efficacy of convalescent plasma therapy in COVID 19.

f) Role of other Immuno-modulator drugs:

Given the important role, the immune response plays in the complications of COVID-19, active clinical trials are evaluating immune-modulatory drugs such as IL-6 receptor antagonists like Sarilumab and Tocilizumab. In patients with "cytokine storm," characterized by marked elevation in inflammatory markers, use of IL-6 receptor antagonists is being considered, preferably in the context of a clinical trial, although these medications can increase risk of secondary infections.

g) Role of BCG vaccine

The 100-year-old BCG vaccine has received increasing attention as a possible treatment of COVID 19. The reason for the excitement is that early analysis patterns in data seem to indicate that in countries that have had mass immunization programmes with the BCG vaccine, the spread of Covid-19 seems to be slower. The idea that BCG offers protection against the novel coronavirus, or SARS-CoV-2, seems to stem from the vaccine's ability to induce a trained immune response, where the immune system of someone inoculated against the tuberculosis bacteria grows the ability to fight off other pathogens, including parasites and viruses. The Haffkine Institute in India will soon begin clinical trials of the Bacillus Calmette-Guérin (BCG) vaccine to see its efficacy in the treatment of Covid-19.

h) Should ACE inhibitors be discontinued in COVID-19?

There has been a debate on whether ongoing treatment with ACE inhibitors (ACEI) and ARB's could worsen the prognosis in COVID 19. This is due to the fact that SARS-CoV-2 uses ACE2 as a target to enter human cells and ACEI and ARB's can increase the expression of ACE2. This has led to concern that the use of ACEIs and ARBs will increase patient susceptibility to viral host cell entry and propagation. There has been considerable evidence in animal models as well as some evidence in humans showing increased expression of ACE2 in the heart, brain, and even in urine after treatment with ACEI & ARBs; however, there is limited evidence showing changes in serum or pulmonary ACE2 levels. More importantly, the significance of ACE2 expression on COVID-19 pathogenesis and mortality is not specifically known. So, the speculation that ACE-inhibitors or ARBs treatment can make infections worse in the context of COVID-19 is not supported by clinical evidence. Clinical trials are currently underway to generate more data on this issue. However, the expert bodies have strongly recommended that physicians and patients should continue treatment with these drugs because there is no clinical or scientific evidence to suggest that treatment with ACEIs or ARBs should be discontinued because of the COVID-19 infection.

References:

1. Sanders JM, Monogue ML, et al. Pharmacological treatments for coronavirius disease 2019: A review. JAMA. Online April 13, 2020. Doi:10.1001/jama.2020.6019

2. Advisory on the use of HCQS as prophylaxis of SARS-CoV-2 infection. Available from https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf

Recent news/Updates from the world of medicines ……..

Oxford's Covid-19 Vaccine – ChAdOx1 n CoV-19 started human trial in United Kingdom

Oxford University's Jenner Institute will start human testing with a Covid-19 vaccine, the UK government said in a coronavirus press conference. The Oxford team – led by Professor Sarah Gilbert, is testing ChAdOx1 nCoV-19, a candidate based on a chimpanzee adenovirus modified to include the spike or 'S' protein on the surface of SARS-CoV-2, the virus that causes Covid-19. The vaccine is made from a weakened version of a common cold virus (known as an adenovirus) from chimpanzees that has been modified so it cannot grow in humans.

Teprotumumab approved for Thyroid Eye Disease in All, including Smokers

Teprotumumab is the first-ever medication approved specifically to treat thyroid eye disease; and works in patients regardless of age, gender, and smoking status, new research finds. Prior to that, therapy typically involved steroids or in severe cases, surgery. Teprotumumab is a fully human monoclonal antibody inhibitor of the insulin-like growth factor-1 (IGF-1) receptor, and was approved by the US Food and Drug Administration in January 2020. Blocking the IGF-1 receptor leads to reduced inflammation and reversal of retro-orbital tissue expansion and Hyaluronan production in the eye orbit. Previously reported pooled data from phase 2 and phase 3 of the randomized, placebo-controlled OPTIC trial involving 171 patients showed significantly greater reductions in proptosis, as well as diplopia, and clinical symptoms of inflammation with Teprotumumab versus placebo. Teprotumumab is given as an infusion once every 3 weeks for a total of eight infusions.

Is Sepsivac can be a game changer against Covid-19 in India?

CSIR is currently testing Cadila Pharmaceuticals' "Sepsivac" against COVID-19. It is currently testing a "repurposed" vaccine against Covid-19 in a Phase 2 trial. This treatment was developed as a result of a partnership between CSIR and Cadila Pharmaceuticals many years ago. This immunotherapy treatment, which boosts "innate immunity", was initially approved by the Drug Controller General of India (DCGI) for gram negative sepsis. The trial is being conducted on 50 patients at the All India Institute of Medical Sciences (AIIMS), New Delhi, AIIMS Bhopal, and Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh.

TeleMedicine – Online Prescription at the time of Pandemic…..

Telemedicine means 'healing from a distance'. It is defined as 'The delivery and facilitation of health and health-related services including medical care, provider and patient education, health information services, and self-care via telecommunications and digital communication technologies.

This includes facilitating access to healthcare to both privileged and underprivileged populations, providing faster, cheaper and better communication for treatment, follow-up by experts and to store records. It helps remove geographical barriers to healthcare, especially by reaching distant areas poorly connected by any means of transport. Telemedicine can reduce the burden on the secondary hospitals. Some years ago, the concept of telemedicine and virtual consultation was considered experimental and futuristic. In the present world, it is now a reality and emerging as an important tool for patients in remote locations with limited access to standardized and specialized healthcare services.

With advances in technology, there is better accessibility and affordability of tools of telemedicine. It is also becoming a tool for convenience in healthcare. An important factor responsible for growth in this field is the increasing use of mobile phones. The presence of health applications enables patients to monitor their health status on their own. This proactive approach leads them to use alternative ways to get healthcare services such as telemedicine.

Disasters and pandemics pose unique challenges to providing health care. Though telemedicine will not solve them all, it is well suited for scenarios in which medical practitioners can evaluate and manage patients. In the scenarios of pandemics and disasters, sessions of telemedicine can reduce the risks to both health care workers and patients, and thus prevent the transmission of infectious diseases. On the other hand, institutions invested in telemedicine help to increase the available human resource and allocate them at the respective hospitals to provide physical care for patients in the time of crisis like Covid-19.

With Covid-19 cases spreading across the country, India formally recognised the practice of telemedicine recently. The government's new "telemedicine practice guidelines" legitimise the practice of remote consultations. This could pave the way for widespread adoption of telemedicine not only during this crisis but also in the future. The telemedicine guidelines, prepared by the Medical Council of India (MCI) board of governors and the government think tank NITI Aayog, provide doctors with practical guidance on the process of remote consultations.

One of the important aspects of telemedicine is prescribing medications. The registered medical practitioners (RMP), at his/her professional discretion and same professional accountability can prescribe medications via telemedicine consultation. If a medical condition requires a particular protocol to diagnose and prescribe as in a case of in-person consult then same prevailing principle will be applicable to a telemedicine consult.

The RMP can prescribe medicines as per the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations and shall not contravene the provisions of the Drugs and Cosmetics Act and Rules. The RMP shall provide photo, scan, and digital copy of a signed prescription or e-Prescription to the patient via email or any messaging platform. In case the RMP is transmitting the prescription directly to a pharmacy, he/ she must ensure explicit consent of the patient that entitles him/her to get the medicines dispensed from any pharmacy of his/ her choice.

Further, RMP may prescribe medicines via telemedicine ONLY when RMP is satisfied that he/ she has gathered adequate and relevant information about the patient's medical condition and prescribed medicines are in the best interest of the patient. There are certain limitations on prescribing medicines on consult via telemedicine depending upon the type of consultation and mode of consultation.

The categories of medicines that can be prescribed via tele-consultation will be as notified in consultation with the Central Government from time to time are listed below:

1. **List O**: It will comprise those medicines which are safe to be prescribed through ANY MODE OF TELE-CONSULTATION (TEXT, AUDIO, and VIDEO). These would comprise of medicines which are used for common conditions and are often available 'over the counter'. For instance, these medicines would include, Paracetamol, ORS solutions, Cough& Common cold medicines, Vitamin supplements etc., and medicines that may be deemed necessary during public health emergencies.

2. List A: These medications are those which can be prescribed during the first consult which has to be a VIDEO CONSULTATION. It includes ear drops, eye drops, topical medications etc. This list also includes follow-up medications for chronic illness like Hypertension, DM, and Asthma. This would be an inclusion list, containing relatively safe medicines with low potential for abuse.

3. List B: The medications in this list can be prescribed through ANY MODE OF TELE-CONSULTATION (TEXT, AUDIO, and VIDEO). The list contains medications which are used as add-on therapy to chronic medications to optimise management. It should be in addition to those that have been prescribed during the in-person consultation for the same medical condition. For example adding thiazide to a patient of hypertension who is on Atenolol or addition of Sitagliptin to a patient of DM who is already on Metformin.

Prohibited List: An RMP providing consultation via telemedicine cannot prescribe medicines listed in ***Schedule X*** of Drug and Cosmetic Act and Rules or any ***Narcotic*** and ***Psychotropic*** substance.

References:

1.Ateriya N, Saraf A, Meshram VP, Setia P. Telemedicine and virtual consultation: The Indian perspective. Natl Med J India 2018;31:215–18.

2. BOARD OF GOVERNORS In supersession of the Medical Council of India. Telemedicine Practice Guidelines. New Delhi: Ministry of Health and Family Welfare, Government of India; 25th March 2020. Available from: https://www.mohfw.gov.in/pdf/Telemedicine.pdf

Be Cautious…..Drug Safety Alerts

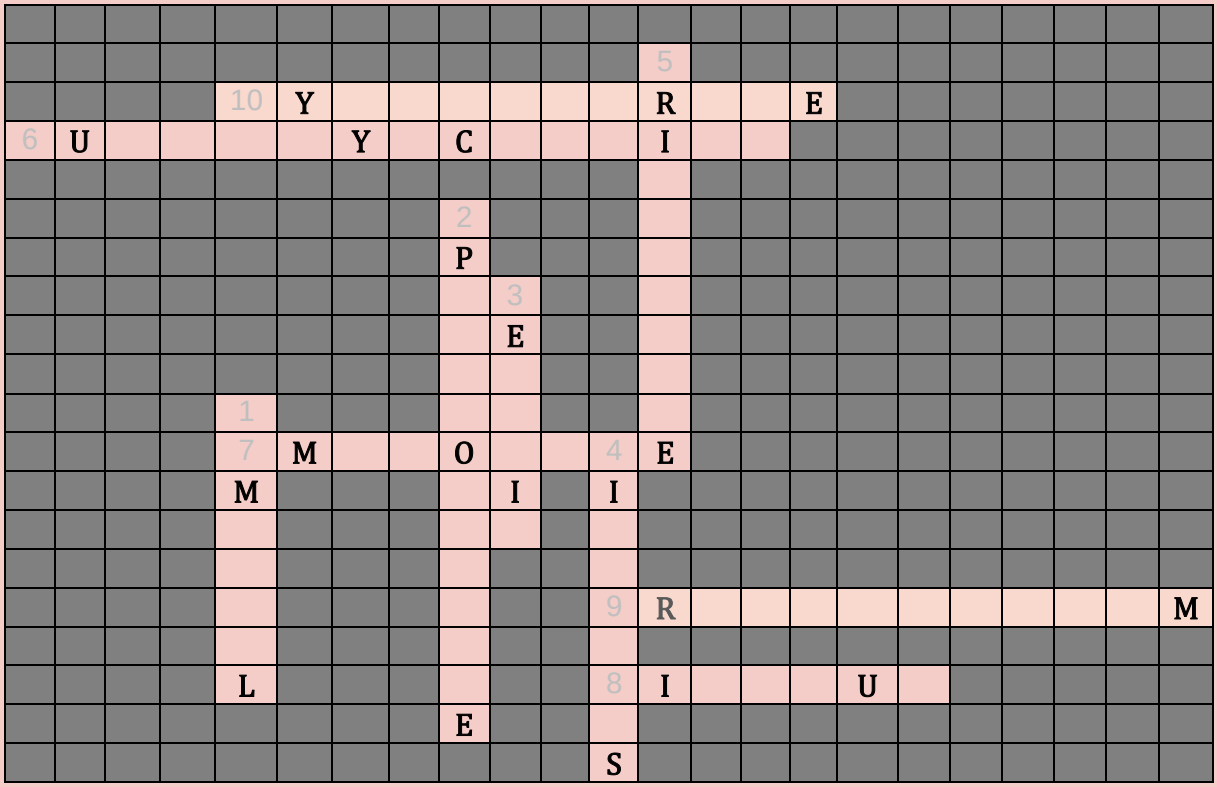
S. No.	Drug	Safety Alerts
1.	Levodopa	Dopamine Dysregulation Syndrome
2.	Ipragliflozin	Shock and Anaphylaxis
3.	Modafinil	Congenital malformations
4.	Olmesartan medoxomil	Interstitial Pneumonia
5.	Gabapentin	Serious Breathing Problems
6.	Cholecalciferol	Insomnia

New Drug Approvals…

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Ozanimod	Sphingosine 1-phosphate receptor modulator	Multiple Sclerosis	0.92 mg/day
2.	Osilodrostat	Cortisol synthesis inhibitor	Cushing's Syndrome	4 mg/day
3.	Isatuximab	CD38-directed cytolytic antibody	Multiple myeloma.	10mg/kg weekly infusion
4.	Rimegepant	Calcitonin gene-related peptide (CGRP) receptor antagonist	Acute treatment of migraine.	75 mg/day
5.	Selumetinib	Inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2)	Neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).	100 mg/day
6.	Tucatinib	Kinase inhibitor	Advanced unresectable or metastatic HER2-positive breast cancer	600 mg/day
7.	Pemigatinib	Selective fibroblast growth factor receptor (FGFR) inhibitor	Locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements	13.5 mg/day
8.	Amisulpride	Dopamine-2 (D2) antagonist	Post-operative nausea and vomiting (PONV).	5 mg IV single dose
9.	Bempedoic acid	Adenosine triphosphate-citrate lyase (ACL) inhibitor	Heterozygous Familial Hypercholesterolemia	180 mg/day
10.	Opicapone	COMT inhibitor	Parkinson's disease during "off" episodes	50 mg/day

Crossword Puzzle…

Hint: *Drugs Causing Hyperkalemia*



Downward

1. Drug which has 'cough' as its one of the adverse drug reaction (8)
2. Diuretic which has 'gynaecomastia' as its one of the adverse drug reaction (14)
3. Anticoagulant which can be used only through parenteral route (7)
4. Drug for CHF obtained from natural source 'Plant' (9)
5. Diuretic acting through 'ENaC (Epithelial Sodium Channels)' at Collecting Duct (11)

Across

6. Short acting depolarizing skeletal muscle relaxant (15)
7. Diuretic which can be used therapeutically through aerosol in cystic fibrosis (9)
8. Drug used in Manic and Bipolar disorders(7)
9. Anti-Microbial agent acts as an anti-folate agent by blocking DHFR enzyme and is usually combined with Sulfamethoxazole (12)
10. Immunosuppressant drug acts by inhibiting Calcineurin (12)

Answers

Downward

1. Ramipril
2. Spironolactone
3. Heparin
4. Digitalis
5. Triamterene

Across

6. Succinylcholine
7. Amiloride
8. Lithium
9. Trimethoprim
10. Cyclosporine