NEPALESE ARMY INSTITUTE OF HEALTH SCIENCES
सर्वे सन्तु निरामया
September 2010

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ISSN 2795-160X (Print)

NAIHS Drug and Therapeutics Bulletin

Published quarterly by Department of Pharmacology, College of Medicine, NAIHS

Vol 1, Issue 2, April-June, 2021

Editorial

The NAIHS Drug & Therapeutics Bulletin "CHARAKA" aims to provide concise, up to date and independent information on various topics related to drug therapy and related areas which will be of interest to medical professionals as well as students. We are very thankful to the readers of the first issue for their very encouraging responses and suggestions. We have tried to put the valuable suggestions given by the readers in action by including some topics that were suggested. We hope to get constructive feedback to this issue too that will help us to improve the upcoming issues of the bulletin.

The Editorial Board

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Immunomodulating Therapies in COVID-19

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. Mortality is mainly due to respiratory failure caused by acute respiratory distress syndrome (ARDS) and multi-organ failure. Various types of immunomodulating therapies including corticosteroids and convalescent plasma therapy (CPT) are being used with the aim of preventing the damage caused by the inflammatory response.

Systemic corticosteroids

It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. Seven randomized controlled trials that included a total of 851 patients, evaluated use of corticosteroids in patients with ARDS. A meta-analysis of these trial results demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI:0.59-0.95) and duration of mechanical ventilation (mean difference, -4.93 days; 95% CI, -7.81 to -2.06 days).[1] According to living guidance issued on 02 September 2020, WHO strongly recommends the use of corticosteroids only for the treatment of patients with severe and critical COVID-19.[2] Dexamethasone, a potent and widely used glucocorticoid with minimal to no mineralocorticoid activity decreases inflammation by suppressing migration of polymorphonuclear leukocytes (PMNs) and reducing capillary permeability; stabilizes cell and lysosomal membranes, and inhibits prostaglandin and proinflammatory cytokines; suppresses lymphocyte proliferation through direct cytolysis, inhibits mitosis, breaks down granulocyte aggregates, and improves pulmonary microcirculation. Its main anti-inflammatory effect is to inhibit a pro-inflammatory gene that encodes for chemokines, cytokines (such as interleukin IL-1, IL-6, TNF, IFN-gamma), cell adhesion molecules, and thus the acute inflammatory response. Meta-analysis of 41 studies (mostly retrospective observational studies, and case series) had previously concluded that there is increased mortality with the use of corticosteroids with delayed recovery and a longer hospital stay.[3] However, the randomized evaluation of COVID-19 therapy (RECOVERY) trial, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19 with 2104 patients in dexamethasone arm, concluded that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support but there is no benefit (and the possibility of harm) among patients who did not require oxygen.[4] A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (e.g. 50 mg every 8 hours), or 40 mg of prednisone or prednisolone, or 32 mg of methylprednisolone (e.g. 8 mg every6 hours or 16 mg every 12 hours). It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.[2]

Inhalational glucocorticoids

Inhalational glucocorticoids are widely used for chronic prophylaxis of bronchial asthma and steroid responsive chronic obstructive pulmonary disease for their local anti-inflammatory effect with minimal systemic adverse effects. Based on reports of significantly lower proportion of patients with chronic respiratory disease admitted to hospital with COVID-19, the hypothesis that use of inhaled glucocorticoids among these patients was responsible for preventing serious disease in COVID-19 patients was made and an open-label, randomized controlled trial was conducted with budesonide dry powder inhalation using a turbohaler at a dose of 800 micrograms, 12 hourly until symptom resolution in the active treatment group This trial concluded that early administration of inhaled budesonide reduced the need of urgent medical care and also reduced time to recovery after early COVID-19. As inhalational glucocorticoids are widely available and relatively safe, it can be a breakthrough in management of early COVID-19.[5]

Convalescent plasma therapy (CPT)

The proposed mechanism of benefit from convalescent human plasma derived from survivors of the coronavirus is the transfer of passive immunity in an effort to restore the immune system during critical illness and neutralize the virus to suppress viremia. As per the COVID-19 treatment guidelines by NIH, on August 23, 2020, the FDA issued an emergency use authorization (EUA) for convalescent plasma for the treatment of hospitalized patients with COVID-19 based on retrospective, indirect evaluations of efficacy generated from a large expanded access program (EAP). The EAP allowed for the use of convalescent plasma regardless of titer. The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of COVID-19 convalescent plasma due to potential confounding, the lack of randomization, and the lack of an untreated control group. On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma and only for the treatment of hospitalized patients with COVID-19 early in the disease course or hospitalized patients who have impaired humoral immunity.[6] Benefits of CPT are reported as lessening of the hospital stay, rapid resolution of fever, relief of dyspnea, regulation of oxygen saturation, radiological improvement, and overall reduction in viral load. Hypersensitivity reactions like chills, transitory red spots on the face, fever, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TALI), and likely deterioration of symptoms in some critical cases have been reported. CPT is normally safe for donors, but some

adverse effects like dehydration, dizziness, fatigue, fainting, and light headedness as plasma contains water, nutrients, and salts may be anticipated.[7] A multi-center, retrospective case control observational study from India concluded that CPT was associated with reduced mortality in COVID-19 elderly patients admitted in ICU, above 60 years of age, particularly females, those with comorbidities and especially those who required some form of ventilation.[8] Recent meta-analyses that included 10 randomized controlled trials concluded that early transfusion (within 3 days of hospital admission) of higher titer plasma is associated with lower patient mortality favoring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized patients with COVID-19.[9] Formal results of clinical trial of CPT in Nepal are yet to be published.

Interferons

In response to infections, there is mobilization of the innate immune system to rapidly produce interferons (IFNs) specifically IFN-α and IFN-β, to defend against viral infection. However, several studies demonstrated that the excessive activation of IFN-α signaling pathway might cause the uncontrolled inflammatory responses, which is positively correlated with the disease severity. [10] During the 2002 SARS outbreak, it was observed that after viral inoculation, SARS-CoV was able to effectively evade upregulation of IFNs in human macrophages. This allowed for continued viral replication due to suppression of the innate immune response. A study comparing a total of 22 patients treated with lopinavir alone and 19 patients with combined therapy with subcutaneous injection of IFN alpha-2b in patients diagnosed with laboratory confirmed COVID-19 infection showed that the average length of hospitalization in the combination group was shorter than that of LPV/r group (16±9.7 vs 23 ±10.5 days; P=0.028). Furthermore, the days of hospitalization in early intervention group decreased from 24±8.5 days to 10± 2.9 days compared with delayed intervention group (P=0.001). Combined therapy with IFN alpha-2b also significantly reduced the duration of detectable virus in the upper respiratory tract. No patient in each group was transferred to ICU or died during the treatment. There was no significant difference in the adverse effects profile between two groups.[11] A phase 2, randomized, open-label study, COVID-19 with moderate symptoms PEG IFN-α2b with standard of care (SOC)compared with SOC reported significant improvement in clinical status on day 15 most likely due to faster viral reduction compared to SOC. The reported adverse effects s in the PEG IFN-α2b plus SOC treatment group in patients with COVID-19 were headache, vomiting, breathlessness, dryness in the mouth, hypoxia, and nausea.[12] A randomized and double-blind phase 2 pilot trial conducted in the UK evaluated the inhaled IFN-β-1a in patients with COVID-19. Compared to the placebo group, the patients receiving nebulized IFN-β-1a had decreased the odds of developing severe disease and shown significant clinical improvement.[13]

Baricitinib

Baricitinib reversibly and selectively inhibits JAK1 and JAK2 with less inhibition of JAK3 and tyrosine kinase. Inhibition of JAK results in inability of signal transmission from cytokine or growth receptors resulting in decreased hematopoiesis and immune cell function. This inhibition of signal transmission prevents phosphorylation and thus activation of signal transducers and activators of transcription (STAT) proteins. Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells. Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-COV-2 but an antiviral effect was not confirmed. On November 19, 2020, the USFDA issued an Emergency Use Authorization for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[14] Immunosuppressive effects of baricitinib may be detrimental during acute viral infections by delaying viral clearance and increasing vulnerability to secondary opportunistic infections. The lack of reliable biomarkers to monitor patients' immune status as illness evolves complicates deployment of immunosuppressive drugs like baricitinib. Furthermore, baricitinib carries the risk of increased thromboembolic events, which is concerning given the proclivity towards a hypercoagulable state in patients with COVID-19.[15]

Tocilizumab

Viral replication activates the innate immune system to secrete various signaling proteins such as interleukins that results in hyperinflammation and may cause lung damage. Interleukin-6 is a key inflammatory protein involved in this pathway. Tocilizumab is a recombinant humanised monoclonal antibody that inhibits binding of IL-6 to both membrane and soluble IL-6 receptors. It is FDA approval for chimeric antigen receptor (CAR)-T cell-induced cytokine release syndrome (CRS), giant cell arteritis, rheumatoid arthritis, and polyarticular or systemic juvenile idiopathic arthritis. Tocilizumab binds to IL-6 receptors, thereby blunting cell signaling and effectively downregulating the excess inflammatory response. Infusion reactions causing hypertension, headache, and skin reactions within 24 hours of administration were reported after administration of tocilizumab.[16] In hospitalized COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids. The primary outcome, all-cause mortality within 28 days of random assignment, occurred in 35% of patients allocated to usual care and 31% of patients allocated to tocilizumab

(rate ratio 0·85; 95% CI, 0·76–0·95; p=0·0028). Patients in the tocilizumab group were also more likely to be discharged from the hospital within 28 days in comparison to patients in the usual care group. Importantly, the 28-day mortality rate of 31% in the tocilizumab group, although lower than the placebo group, remains high and it is unclear whether a reduction in 28-day mortality will translate into longer-term mortality benefit.[17, 18] Sarilumab, another anti-IL-6 antibody, is currently under evaluation for the treatment of COVID-19.

Conclusion

Except for corticosteroids, the other immunomodulating treatments are not widely available and costly. The use of systemic corticosteroids is currently recommended only for the treatment of patients with severe and critical COVID-19 cases. The outcome data regarding the use of immunomodulating therapies in the treatment of COVID-19 and findings, although not conclusive, are suggestive of decreasing the mortality and reducing length of hospital stay especially in severe COVID-19 cases. Selection of most appropriate patients may be the key in success of immunomodulating therapies. More outcome studies on such therapies are needed for definitive and specific conclusions.

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Update on Treatment of Enteric Fever

- Chloramphenicol, amoxicillin, and trimethoprim-sulphamethoxazole were first-line choices before the 1990s. Multidrug resistance i.e., resistance to these three antimicrobials, led to use of fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin) for enteric fever. High rates of fluoroquinolone resistance are now reported in South Asia and increasingly in Africa.
- Extended spectrum cephalosporins including cefixime and ceftriaxone, and azithromycin are now recommended options. Cefixime and ceftriaxone are associated with higher rates of relapse. Resistance to all three agents is also emerging.
- Since a large outbreak of extensively drug resistant typhoid (resistant to ciprofloxacin, ceftriaxone, amoxycillin, chloramphenicol, and trimethoprim-sulphamethoxazole) in Pakistan in 2016, the treatment choice for such infections has shifted to oral azithromycin or parenteral meropenem.

First Line Antimicrobial treatment options for enteric fever

1. Uncomplicated enteric fever:

a. Unknown susceptibility→ Azithromycin 20 mg/kg (total daily dose) for 7 days

b. Fully susceptible→ Ciprofloxacin 20 mg/kg (total daily dose) for 7 days

c. Multidrug resistant→ Ciprofloxacin 20 mg/kg (total daily dose) for 7 days

d. Quinolone resistant→ Azithromycin 20 mg/kg (total daily dose) for 7 days

e. Extensively drug resistant→ Azithromycin 20 mg/kg (total daily dose) for 7 days

2. Severe enteric fever requiring parenteral treatment

a. Unknown susceptibility→ Ceftriaxone 50-75 mg/kg (total daily dose) for 10-14 days

b. Fully susceptible→ Ciprofloxacin 20 mg/kg (total daily dose) for 10-14 days

c. Multidrug resistant→ Ciprofloxacin 20 mg/kg (total daily dose) for 7 days

d. Quinolone resistant→ Ceftriaxone 50-75 mg/kg (total daily dose) for 10-14 days

e. Extensively drug resistant→ Meropenem 60 mg/kg (total daily dose) for 10-14 days

3. Regimens proposed for eradication of chronic carriage (dependent on susceptibility of the isolate)

a. Amoxicilllin susceptible→ Ampicillin 100 MG/KG FOR 90 DAYS OR amoxicillin with probenecid 30 mg/kg for 90 days

b. TMP-SMX (trimethoprim-sulphamethoxazole) susceptible→ TMP-SMX 8-40 mg/kg for 90 days

c. Ciprofloxacin susceptible → Ciprofloxacin 20 mg/kg for 28 days

Note:

- **Unknown susceptibility:** Culture and susceptibility results often unavailable. Empirical treatment should be based on regional knowledge of susceptibility patterns.
- **Multidrug resistant:** resistant to chloramphenicol, amoxicillin, trimethoprim-sulphamethoxazole
- **Quinolone resistant**: non-susceptible to ciprofloxacin (pefloxacin resistant/ciprofloxacin resistant by disk testing)
- **Extensively drug resistant**: resistant to chloramphenicol, amoxicillin, trimethoprim-sulphamethoxazole, ciprofloxacin, and ceftriaxone
- **TMP-SMX**: Inexpensive; may cause allergic reactions and nephrotoxicity, not suitable for children <2 years old or during pregnancy
- **In severe enteric fever** (characterized by delirium, obtundation, coma, or shock) **dexamethasone** may be beneficial (dose 3 mg/kg infused intravenously over 30 min, followed by 8 doses of 1 mg/kg every 6 hours).
- In severe **enteric fever with intestinal perforation and peritonitis**, a laparotomy is recommended to identify and close the perforation(s) and to perform cleaning of the peritoneal cavity.

Conclusion: Culture proven *S. typhi*→ look for antibiotic susceptibility.

- Unknown susceptibility→oral azithromycin or IV ceftriaxone
- Fully susceptible→ IV ciprofloxacin
- If quinolone resistant → IV ceftriaxone

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Adverse effects of Statins

Statins are a widely prescribed class of drugs and are in fact the hallmark of drug therapy of dyslipidemias. They act as competitive inhibitors of HMG-CoA (hydroxymethylglutaryl-coenzyme A) reductase, the rate-limiting enzyme in the cholesterol biosynthesis.[1] Despite the widespread use of statins, discontinuation is an ongoing issue. Statin-associated muscle symptoms which are the most well-documented side effect of statins is a major reason. In addition, other more serious adverse effects of statins may also occur, with the next most established being new-onset type 2 diabetes mellitus for which the mechanisms are far less clear. Other side effects include neurological and neurocognitive effects, hepatotoxicity, renal toxicity, and others (gastrointestinal, urogenital, reproductive), which currently have no established validity.[2] This review focuses on the above adverse effects.

It is important to consider all of the manifestations of statin toxicity and intolerance, which can significantly impact adherence to therapy and subsequent cardiovascular risk. Mechanistically, statin toxicity is thought to arise because of HMG-CoA reductase inhibition effects, direct cellular and subcellular effects, or a combination of both. Other possible causes include genetic factors, drug-drug interactions, vitamin D status, and other metabolic or immune effects. Adverse side effects have generally been shown to be class, dose, time, age, sex, and comorbidity dependent; however, considerable variability exists. Age is considered the leading predisposing risk factor because of the likely presence of multiple comorbidities (renal or liver dysfunction), concomitant drug use that may interfere, decreased body mass, cognitive impairment, and a decreased resistance to other stressors.[2]

Statin-associated muscle symptoms (SAMSs)

SAMSs are by far the most prevalent and important adverse event, with up to 72% of all statin adverse events being muscle related.[2] These can present as myalgia, myopathy, myositis with elevated creatine kinase (CK), or at its most severe, life –threatening rhabdomyolysis, with some people reporting additional joint and abdominal pain. Other skeletal-related side effects include tendinopathies and tendon disorders, as well as arthralgias.[1,2]

Clinical presentation

Regardless of the definition, SAMs usually presents as a symmetrical (bilateral) condition that affects the large proximal muscles, particularly of the lower extremities. Symptoms can occur at rest or shortly after exercise and usually occur within 1 month of initiation of therapy or an increase in dose. Beginning at asymptomatic CK elevation, they include tolerable and intolerable myalgia, myopathy, severe myopathy, rhabdomyolysis, and autoimmune-mediated necrotizing myositis. However, it is now recognized that muscle adverse events do not present as a continuum that begins with myalgia and progresses to more severe forms, thus requiring each event to be categorized using standard definitions. From a clinical viewpoint, SAMSs can be divided into 4 groups: (1) rhabdomyolysis characterized by high creatine kinase (CK) concentrations (>100-fold the upper limit of normal [ULN]), myoglobinuria, and renal impairment; (2) myalgia or mild hyperCKemia (<5× ULN); (3) self-limited toxic statin myopathy (CK levels between 10 and 100 ULN); and (4) myositis or immune-mediated necrotizing myopathy with HMG-CoA reductase antibodies and CK levels between 10 and 100× ULN. Muscle toxicity is classed as either toxic or immune related. Immune-related statin-induced muscle toxicity is driven by both inflammatory and noninflammatory pathways. Inflammatory myopathies, while rare, are characterized by large increases in CK levels, a myopathic pattern on electromyogram and inflammatory infiltrates on muscle biopsy. The condition usually resolves with discontinuation of statin therapy and immunosuppressive therapy. The prevalence of SAMS differs between statin classes, with the highest risk associated with lipophilic statins such as simvastatin, atorvastatin, and lovastatin because of their ability to non-selectively diffuse into extrahepatic tissues such as skeletal muscle. In contrast, hydrophilic statins such as pravastatin and fluvastatin have less muscle penetration and therefore lower risk of SAMS.[2]

New-onset type 2 diabetes mellitus

Incidence of new-onset type 2 diabetes mellitus with statin treatment appears to be more common in patients with preexisting risk factors, including elevated body mass index and glycated hemoglobin or impaired fasting glucose. It has been observed for both hydrophilic and lipophilic statins and appears to occur more frequently in older patients and those on high-dose statin therapy. Mechanistically, the incidence of new-onset type 2 diabetes mellitus is not known but may be related to both on-target and off-target action, including effects on body weight, body mass index, adipocyte differentiation, blood glucose homeostasis via gluconeogenesis and the insulin signaling cascade, changes in circulating free fatty acids or hormones such as adiponectin and leptin, as well as impaired β-cell function.[2]

Neurological and neurocognitive conditions

Neurological conditions that have been associated with statin use include hemorrhagic stroke, cognitive decline, peripheral neuropathy, depression, confusion/memory loss and aggression, and personality changes. It is unclear whether these are because of the direct action of statins given the blood-brain barrier's selective permeability to substrates and the brain's self-sufficiency when it comes to endogenous cholesterol synthesis. Lipophilic statins are thought to have a higher risk because of their increased ability to cross the blood-brain barrier; however, it should be noted that these effects may not be specific to statins per se and instead a result of low cholesterol levels. Reductions in serum lipid levels have been proposed to negatively affect the formation of neuronal

cell membranes, myelin sheath, and nerve synapses. Reduced cholesterol availability for neurons can then contribute to lower serotonin activity through reduced receptor expression, which can result in changes in behavior control and adverse psychiatric effects.[2]

Hepatotoxicity

Early clinical trials of statins revealed elevations in aminotransferases in up to 2% of patients despite only rare observation of clinically apparent liver injury. Asymptomatic rises in hepatic enzyme activity, with elevated aminotransferase activity >3× the ULN, is a common side effect that normally resolves with dose reduction and is not associated with histopathology changes or liver toxicity in the absence of increased bilirubin or dysfunction. When combined with increased bilirubin, statin discontinuation and monitoring of liver function is necessary. More serious, but rare hepatotoxicity, may present as asymptomatic elevation in serum transaminases, hepatitis, cholestasis, and acute liver failure. Current evidence suggests statin therapy to be safe in patients with nonalcoholic fatty liver disease and may confer more efficient treatment of viral hepatitis and reduced risk of cirrhosis and hepatocellular carcinoma.[2]

Renal toxicity

Controversy still exists about the effects of statins on renal function. Mild transient proteinuria is sometimes seen with high-dose statin treatment, but this is not associated with impaired renal function. [2]

Other statin-mediated adverse effects

Other statin-mediated adverse events include cataracts, gastrointestinal effects, urogenital health effects, gynecomastia, and reproductive effects, most of which have been purported to be as a result of reduced production of intermediate and end products of the mevalonate pathway. Thyroid disease, while not thought to be because of statin toxicity per se, may contribute to statin intolerance, particularly with respect to SAMS. [2]

Statins may be associated with reductions in androgens as they inhibit production of the substrate required for local synthesis. Fetal exposure to statins may also result in adverse effects, and this is particularly relevant when considering patients with familial hypercholesterolemia who require lipid-lowering therapy from an early age. An analysis of pregnant women found that statin exposure during the first trimester was associated with an increased risk of fetal ventricular septal defect, and there was a higher incidence of congenital cardiac abnormalities in pregnancies exposed to statin therapy. [2]

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Food-Drug Interactions

Natural foods and vegetal supplements have recently become increasingly popular for their roles in medicine and as staple foods[1]. In this regard, their increased consumption has raised concerns over the potential interactions between food products and drugs particularly in patients undergoing chronic therapy. Although the effect of food is not clinically important for many drugs, there are food-drug interactions which may have adverse consequences. Often these interactions can be avoided by advising the patients to take their medicines at the same time with respect to meals[2].

The influence of dietary substances on drug effects depends on numerous variables ranging from physicochemical properties of the drug to host factors such as enzymes and transporters in the gastrointestinal (GI) tract as well as in the entire body. The interactions may affect not only blood levels of drugs through pharmacokinetic change (absorption, distribution, metabolism and excretion: pharmacokinetic interactions), but also the actual effects of drugs (pharmacodynamic interactions) [1].

Pharmacodynamic interactions

Some foods attenuate or enhance drug effects and toxicity by interfering with drug actions, mechanism and pharmacodynamics of the drug. Examples of pharmacodynamic food –drug interactions are:

The anti-coagulant warfarin antagonizes vitamin K1 recycling leading to the depletion of active vitamin K1. However, green leafy vegetables or "greens" contain large amounts of vitamin K1 reversing its depletion. Similarly, renin- angiotensin system inhibitors increase plasma potassium [K+] levels due to a reduction in aldosterone activity. However, foods rich in [K+] such as oranges and bananas may cause hyperkalemia resulting in cardiac arrest and death due to myocardial arrhythmia.

Pharmacokinetic interactions

Pharmacokinetic interactions can cause an increase or decrease in the blood level of the drugs and therefore, their effects and toxicities.

A) Pharmacokinetic interactions caused by physicochemical properties:

The physicochemical properties of food products may cause changes in the pharmacokinetics of drugs by chemically binding to the drug and converting it into an insoluble salt that is not easily absorbed. For example; proteins in food would bind to the antiepileptic agent, Phenytoin, resulting in reduced phenytoin absorption and potentially reduced seizure control. On the other hand, foods rich in fat can increase drug absorption by improving the solubility of lipid soluble drugs, such as some antiretroviral protease inhibitors like saquinavir and atazanavir. Some examples of the effect of specific dietary components on selected drugs are listed in the table below [2]:

B) Pharmacokinetic interactions related with enzymes and transporters:

This relates to the pharmacokinetic interactions that occur when food alters the activities of the enzymes and/or transporters involved in the drug pharmacokinetic processes. To investigate these pharmacokinetic interactions, the enzymes or transporters involved in the interaction and the active compounds contained in the food working on them must be clarified. However, food products contain too many compounds making it difficult to investigate all of them. A number of studies have investigated the effects of phytochemicals on drug metabolism. It has however been challenging to conclusively indicate the effects of phytochemicals on drug metabolism because of the discrepancies observed between in vitro and in vivo studies.

C) Metabolizing enzymes and presence in the GI enterocytes

(i) CytochromeP450

Cytochrome P450s are a superfamily of enzymes involved in the Phase 1 metabolism of xenobiotics and endogenous compounds. The three families of CYP1, CYP2 and CYP3 and CYP3A4, CYP2C9 and CYP1A2 from these families constitute the major liver enzymes in the human body. These enzymes metabolize drugs before they reach the systemic circulation resulting in decreased bioavailability of the drugs. CYP3A is responsible for oxidative metabolism of more than half of the pharmaceutical products in the market.

(ii) Esterase

Esterases are enzymes that metabolize inactive biological compounds, known as prodrugs, to their active form in the body through hydrolytic cleavage of the ester bond to form active species. Inhibition of enteric esterases by dietary substances leading to increased ester absorption has been shown in rats but the clinical significance of it remains under investigation.

D) Transporters and presence in GI enterocytes

Several types of transporting proteins are involved in the absorption and distribution of macromolecules including drugs in the body.

(i) P-glycoprotein

P-glycoprotein (P-gp) is a membrane glycoprotein that protects cells by extruding toxic substances from them. P-gp is highly expressed in tissues that have direct contact with xenobiotics such as the epithelium of gastrointestinal tract, the renal proximal tubule (brush

Specific foods	Medicine (Class)	Mechanism of interaction	Implications
Vitamin K rich foods	Warfarin	Dietary intake of Vitamin K rich foods may disinhibit the action of warfarin	Failure to achieve desired INR level
Potassium rich foods and supplements	ACE inhibitors, potassium, diuretics, angiotensin receptor antagonists	Foods and accompaniments high in potassium can increase the serum potassium level when taken along with these drugs	Hyperkalemia
High protein meal	Levodopa	Reduce the cerebral uptake of levodopa	Potentially reduced clinical efficacy of levodopa
Tyramine rich foods	Monoamine oxidase inhibitors	Tyramine rich foods indirectly lead to increased release of catecholamines	Significant risk of hypertensive crisis
Calcium rich foods	Tetracyclines, fluoroquinolones	Co-administration of calcium rich foods and supplements results in chelation and reduced drug absorption	Risk of therapeutic failure

border level), the canalicular surface of hepatocytes, and the endothelial cell surface of the blood-brain barrier. Some dietary supplements may have a major effect on P-gp mediated transport and interfere with anticancer therapies.

(ii) Organic anion transporting polypeptide

In contrast to P-gp, organic anion transporting polypeptides (OATPs), a type of membrane transport proteins, facilitate the uptake of a number of endogenous compounds (e.g., bile acids, hormones) and drugs. Of the 11 human OATP family members, OATP1A2 and OATP2B1 have been reported to be expressed on the apical membrane of enterocytes. A decrease in the drug concentration in systemic circulation could be attributed to the inhibition of an apically located intestinal uptake transporter.

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Article Summary: Up-to-date Use of Honey for Burns Treatment. Ann Burns Fire Disasters. 2014; 27(1):22-30.

Made by bees from the nectar of flowers, used since ancient times to treat wounds and burns, with growing interest from the international scientific community, honey has been the subject of many specialized studies and communications. It is one of the most complex and valuable natural biological products used since ancient times, both in nutrition and medicine (through internal and external means). Among other medical uses, honey has served in wound care since ancient times.

The ideal topical preparation for wounds should meet the following criteria:

- Bactericidal and fungicidal action, rapid set up and wide spectrum, even under the unfavorable situations of heavy exudation or wound infection;
- Enhancement and acceleration of the physiologic process of wound healing (granulation, epithelialization, contraction);
- No local or systemic adverse effects (allergy, toxicity, etc.), even if applied for prolonged periods;
- Moderate cost, even if applied twice a day;
- Patient comfort, ease of application, pain reduction; and
- Patient and healthcare compliance.

According to performed studies, the topical use of honey for wounds and burn care meets most of the above-mentioned features.

Antimicrobial activity

Honey has proven to have a broad-spectrum anti-infectious action against at least 80 species of micro-organisms including Gram-positive and Gram-negative bacteria, aerobes and anaerobes, some fungal species of Aspergillus and Penicillium and all the common dermatophytes. This includes bacteria multi- resistant to antibiotics, such as Pseudomonas, Acinetobacter, methicillin-resistant (MRSA) and coagulase-negative Staphylococcus aureus, with a minimum inhibitory concentration (MIC) generally below 10%, usually inferior to that present in wounds where the honey was applied.

The increasing interest in the use of honey in infected wounds is strengthened by the widespread development of bacterial resistance to antibiotics, as well as evidence that honey is fully effective against such antibiotic- resistant bacteria. Unlike with antibiotics, studies have shown no development of bacterial resistance and no emergence of mutants resistant to honey. There was no loss of bacterial sensitivity to honey over time and no appearance of bacteria resistant mutants. In many cases, honey acted where other antibacterial therapies failed, possibly because honey effectively penetrates aggregated bacteria in biofilms, a situation where antibiotics and silver dressings proved ineffective. Honey possesses a level of osmolarity which is able to inhibit microbial growth. But the antibacterial quality of honey is also due to other factors. Honey contains an agent that was called "inhibine" before its identification as hydrogen peroxide. This is a well-known antimicrobial agent that is produced by the enzyme glucose oxidase in honey, secreted by the hypopharyngeal glands of bees. Under the action of glucose oxidase, glucose oxidation makes gluconolactone and hydrogen peroxide.

Wound healing activity

Studies have also revealed an intrinsic antioxidant activity of honey, by controlling free radicals and Reactive Oxygen Species (ROS). The ROS act as messengers that amplify the inflammatory response and this process can be blocked by antioxidant substances present in honey at a high level. Also, ROS produced by phagocytes in inflamed tissues activate proteases that are normally inactive and their activated forms digest extracellular matrix and cell growth factors that are essential for tissue repair.

Besides its own anti-infectious, anti-inflammatory and antioxidant actions, honey creates a physical barrier and moist local environment, due to its high viscosity and to the drawing of fluids by osmosis. This promotes healing of burn wounds because wounds heal faster when kept moist as opposed to when they are left to dry out and form a scab. A moist environment ensures the growth of epithelial cells, the contraction of fibroblasts to approach the wound edges, as

well as non-adherence of dressings to the wound, leading to easy and painless dressing changes, without the risk of breaking newly formed epithelium. Also, a local environment allows the protein-digesting enzymes in the wound tissues to work and loosen any scab and dead tissue.

Honey is further known to have a wound debriding action, as found in clinical trials. Honey activates plasminogen and increases plasmin enzyme activity, which lyses fibrin attaching slough, by suppression of the macrophage plasminogen activation inhibitor. Plasmin digests fibrin, which attaches debris on wound surface, but does not digest collagen extracellular matrix, which is necessary for tissue repair.

Local nutritional support

Honey also has a nutritional action in the wound, indirectly through osmotic flow of lymph, which brings nutrients needed for healing, but also directly through an intake of easily metabolized carbohydrates, amino acids, vitamins and minerals. Studies have shown that wounds heal faster if they are supplied with a mixture of nutrients. Honey provides glucose support for epithelial cells, leukocytes and for the process of glycolysis. The epithelial cells require a reserve of carbohydrates for energy migration over the wound surface to restore epithelial sheath. Leukocytes create the respiratory (oxidative) burst that produces hydrogen peroxide, which is the dominant component of macrophages antibacterial activity. Finally, glycolysis is the major mechanism of energy production by macrophages, allowing them to function in damaged tissues and exudates where oxygen is often limited.

In addition, the high osmolarity of honey causes interstitial fluid drainage, thus providing nutritional support for tissue regeneration which can otherwise only occur around points of angiogenesis (seen as granulation). Inducing the osmotic flow will also contribute to lifting and removing waste and debris from the wound, which may even eliminate the need for surgical debridement. It also contributes to the lack of adherence of the dressing to the wound. A fluid layer of honey is in contact with the surface of the wound and it may be slightly raised to allow removal of any residue by rinsing. Thus, dressing changes are painless with no risk of damage or tearing of newly formed tissue.

Other beneficial effects

Studies have also shown high patient acceptability to honey therapy, due to the favorable effects observed in practice: decreased pain, reduced wound size, and deodorizing effects.

How to use honey in burn wounds?

As described in most clinical trials, the following points provide the general guidelines for applying honey:

- First the wound is cleansed with saline. Sometimes it is necessary to make an initial surgical toilet, by opening abscesses, purulent drainage collection and necrotic tissue removal
- Honey is then spread on the wound before being covered with a dry sterile gauze dressing. The amount of honey used varies from a thin layer (applied 2-3 times per day), to a thick layer or, more often, pouring the honey over the wound. Others used bandages soaked in honey, honey spread on gauze or "honey pads". Alginate dressings impregnated with honey are a good alternative to cotton/cellulose dressings, as the alginate converts into a honey-containing soft gel. Wound cavities were either filled with honey-impregnated dressings or filled directly with honey and then covered with gauze.
- Dressing changes, mostly daily, varied from 2-3 times per day to once every 2-3 days, depending also on the appearance and evolution of the wounds (clean wounds with reduced exudate require less frequent dressing changes).
- Liquid honey can be used on large areas (be it naturally fluid or made so through vigorous stirring or by heating below 40°C). Crystallized honey can easily be made fluid through careful heating. Overheating of honey should be avoided, since the enzyme glucose oxidase in honey that produces hydrogen peroxide, a major component of honey's antibacterial activity, is easily inactivated by heat.

Adverse effects

There is a hypothetical risk of wound botulism by applying honey, because it sometimes contains spores of Clostridium. However, no local infections have been reported in the numerous published trials which used unsterilized and unprocessed honey. If the spores would germinate, any Clostridia vegetative cells, being anaerobic, could not survive in the presence of hydrogen peroxide generated in diluted honey. In any case, concerns about a hypothetical risk of wound botulism, considered unacceptable by some, can be overcome by using honey that has been sterilized by gamma irradiation, which kills Clostridium spores in honey, without affecting its antibacterial activity

Conclusion

Preclinical research and clinical studies have shown the efficacy of honey in superficial and partial thickness burns therapy, when compared to other dressing products, making it a viable option as a valuable topical agent in clinical practice. However, as honey also appears to delay healing of partial and full thickness burns when compared to surgical treatment (early excision and grafting), its use requires further exploration.

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Storage of Drugs and other Pharmaceutical Products

Introduction

The pharmaceutical products should be stored under the conditions that prevent contamination and possible deterioration. The deterioration may be due to atmosphere, moisture, heat and light. The storage condition is important as they may impact the quality of the product. High temperature and relative humidity (RH) are the most important factors involved in drug degradation and other factors such as air quality, time and production process characteristics can also have significant impact on the final quality of the product. For many products requiring storage in cool conditions, refrigeration plant is widely used, which needs to be carefully monitored to ensure that the correct temperature is maintained.

All medicinal products must be stored in accordance with the manufacturer's directions and within the terms of product authorization. Particular attention should be paid to protect the drug from contamination, sunlight, UV rays, atmospheric moisture and extreme temperature conditions. During storage, medicines should be retained in the manufacturer's original packaging. Good storage practice is applicable in all circumstances where pharmaceutical products are stored throughout distribution process. The worldwide practice is to adopt WHO guidelines on good storage practices.

Rise in the reaction temperature by 10 °C can double or triple the rate of a chemical reaction and vice versa. After all drugs are chemicals so when storage temperature increases the reaction rate also increases which in turn decreases the shelf life of the drug.

Storage condition specified on the label

Storage conditions for pharmaceutical products of different dosage form i.e., tablet, capsule, emulsion, suspension, injections should be in compliance with the labelling, which is done on the basis of the results of stability testing. Storage condition is always defined and described on the label of the product. Storage areas should be designed or adapted to ensure good storage conditions. For example: improper storage of insulin decreases the potency and hence the pharmacological action of insulin. Patients should also be educated on the proper methods of storage. Insulin is one such labile drug, sensitive to extreme temperatures and sunlight and hence needs to be stored under refrigeration between 2- 8°C.

Storage of vaccines

Vaccines are sensitive biological products that may be less effective, or even destroyed, when exposed to temperatures outside the recommended range. Vaccines exposed to temperatures above or below the recommended temperature range experience some loss of potency with each episode of exposure. All vaccines have a predetermined shelf life and the potency of vaccines is guaranteed by the manufacturers up to the expiry date as stated on the product, if stored within the safe temperature range of between 2°C and 8°C.

Cold chain

The system used for keeping and distributing vaccines and other drugs in good condition is called the cold chain. The cold chain consists of a series of storage and transport links, all designed to keep vaccines within an acceptable range until it reaches the user.

The success of any immunization program depends on administering effective vaccines. Vaccines quickly lose effectiveness if they get too hot or cold during transport and storage. It is therefore essential to maintain an unbroken cold chain for the vaccines from the point of manufacture, during transport and during storage in a refrigerator until they are used to vaccinate someone. In most of the cases, storage temperature should never exceed 8 °C or fall below 2 °C. Vaccines should always be stored in trays in the middle of the refrigerator or freezer, never in the doors. The reason for this is that items stored in the door are frequently exposed to warm temperatures when the unit is opened.

Cold chain equipments

All cold chain equipment has to comply with a set of performance standards defined by the WHO) or national policy. Only proven methods should be used to transport or store vaccines.

The recommended equipment typically used for vaccine storage are:

(a) Cold rooms
(b) Refrigerators
(c) Freezers

For transporting vaccines equipment these are commonly used:

a) Cold boxes
b) Vaccine carriers
c) International containers of various types e.g., ocean active, air-active, air-passive etc.

How to assure cold chain?

Cold Chain Monitor Card (CCM): A heat sensitive indicator in the form of a strip with four windows (A, B, C and D). The indicator operates above 10°C and 34°C. The higher the temperature above the CCM threshold, the color changes to blue which is irreversible even when exposed to lower temperatures again.

Chemical Temperature Indicators: These units are mostly single use devices, with average accuracy. Some chemical monitors can be permanently affected by temperature exposure, while

others are reversible. Advantages of this device is low cost and the size, while disadvantages include low accuracy and limited temperature ranges.

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Potential Immunomodulatory and Antiviral Activity of Curcumin in COVID-19

Curcumin, as an active constituent of rhizomes of *Curcuma longa* (Turmeric, Haledo/Besar in Nepali), is a hydrophobic polyphenol.[1] Turmeric is used mostly in the form of dried powder as a spice in foods as well as medicine for both external and internal use in the Ayurvedic system of medicine. In Ayurvedic medicine, turmeric has been employed to cure a broad spectrum of common ailments, and similar usage has been noted in Chinese traditional medicine.[1,2]

Pharmacological effects

Curcumin has several pharmacological effects such as antioxidant, anticancer, antibacterial, antiviral, and antidiabetic effects as well as anti-inflammatory activity. Other prominent beneficial effects of turmeric include anti-apoptotic, anti-fibrotic, antiemetic, anti-nociceptive, antipyretic and bronchodilator effects. Broad-spectrum antiviral activity and immunomodulatory activity provides a strong rationale for testing curcumin for COVID-19 treatment.[2] Curcumin has been found to interact with spike glycoprotein with a high binding affinity in molecular docking study.[3] Curcumin has been shown to prevent the replication of SARS-CoV and inhibit 3Cl protease in Vero E6 cells. Also, it significantly has an inhibitory activity against the cytopathogenic effect of SARS-CoV in Vero E6 cells. Curcumin was effective against other viruses such as Influenza A virus, HIV, Enterovirus 71(EV71), Herpes simplex virus (HSV), Hepatitis C virus (HCV), and Human papillomavirus (HPV) with several mechanisms that made it valuable for antiviral therapies. In severe COVID-19 infection, pneumonia may cause hypoxemia, which, in turn, disturbs cell metabolism and reduces the energy supply, and increases anaerobic fermentation. Resulting acidosis causes oxygen free radicals to destroy the phospholipid layer of the cell membrane Therefore, treatment with a drug that has antioxidant properties will be good for these patients and curcumin has this effect. Several studies have shown that curcumin is a strong antioxidant. Curcumin (1 mg/kg, 5 mg/kg) increased the superoxide dismutase (SOD) level in acute lung injury induced by intestinal ischemia–reperfusion in mice Furthermore, curcumin (200 mg/kg) reduced malondialdehyde (MDA) level and recovered the levels of xanthine oxidase (XO) and total antioxidative capacity (TAOC) in ventilator-induced lung injury in rats. Similarly, curcumin (200 mg/kg) increased SOD activity and decreased MDA content in the lung in acute injury induced by sepsis. Preclinical studies have shown the beneficial effects of turmeric in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) models. Some of the mechanisms include decreased IL-6 level and myeloperoxidase (MPO) activity, intercellular adhesion molecule-1 (ICAM-1) expression, and bronchoalveolar lavage fluid (BALF) protein in the mice.

Novel formulations of curcumin

Low bioavailability is the major obstacle in attaining the therapeutic potential of oral curcumin. In contrast, pulmonary delivery of curcumin will overcome this limitation and offers several advantages: direct delivery of high concentration of curcumin to the site of infection; direct contact of curcumin with the virus SARS-CoV-2; direct deposition into lower airways and alveolar region; larger surface area for deposition and absorption; lower intra- and extracellular

detoxification enzymatic activity in the pulmonary system. The nanotechnology-based formulation has dramatically eased drug delivery to the pulmonary system. Scientists have developed curcumin encapsulated nano-carriers such as liposomes, niosomes, lipid complexation, micro/nano-emulsions and polymeric nanoparticles. This nano-formulated curcumin could be delivered in dry powder, nebulizer, solution, nasal spray or gel. Curcumin at physiological pH of 7.4 is unstable with a shelf life of 10 min, and the pH of the respiratory tract ranges from 7.2 to 7.4. The nano-formulation of curcumin would be protected from exposure to alkaline pH and thereby improve curcumin's stability at the target site. [4] Report of a clinical trial with curcumin combined with piperine (which increases the bioavailability of curcumin very significantly) on patients with COVID-19 is awaited.[5]

Food and drug interactions

Pre-treatment of both ginger and turmeric juice significantly increases the tacrolimus blood concentrations.[6] Curcumin has been reported to change both the function and expression of the P-glycoprotein (P-gp) and the Cytochrome P450, (CYP3A) enzymes. Curcumin has beneficial interaction with doxorubicin by enhancing antitumor activity and diminishing the adverse effects of doxorubicin.[7]

Adverse effects and precautions

As turmeric has antiplatelet effect and also known to reduce thromboxane formation and reduces incorporation of arachidonic acid into platelet phospholipids, it must be given with caution in patients with thrombocytopenia and platelets disorders. It should also be given with caution with aspirin and warfarin.

Conclusion

Curcumin, as a potential agent, could be considered for prophylaxis as well as treatment of COVID-19 as it has multiple beneficial effects by multiple mechanisms. Intense research is being underway to improve curcumin's bioavailability by developing a formulation to increase its solubility, stability, and absorption. The formulations such as water-soluble curcumin, curcumin nanomicelle, and curcumin plus piperine have increased the bioavailability of curcumin and improved the clinical efficacy of curcumin. Use of turmeric with black pepper as home remedy in respiratory problems is also based on the same principle.

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List of recently approved drugs by the US Food and Drug Administration (USFDA)

S.N.	Drug	Group/Class	Date of Approval	Indications
1	Idecabtagene vicleucel (suspension for iv infusion_)	B-cell maturation antigen (BCMA)	March 26, 2021	Adult patients with relapsed or refractory multiple myeloma
2	Dasiglucagon (Injection)	Glucagon analog antihypoglycemic agent	March 22, 2021	Severe hypoglycemia in diabetes patients aged 6 years and older
3	Ponesimod (Tablet)	Selective sphingosine-1-phosphate receptor 1 (S1P1) modulator	March 18, 2021	Adults with relapsing forms of multiple sclerosis (MS)

S.N.	Drug	Group/Class	Date of Approval	Indications
4	Oritavancin (Injection)	Lipoglycopeptide antibiotic	March 12, 2021 (2nd product; 1st product approved in 2014)	Acute bacterial skin and skin structure infections (ABSSI) caused by designated Gram-positive microorganisms, including methicillin-resistant Staphylococcus aureus (MRSA)
5	Tivozanib (Capsule)	Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI)	March 10, 2021	Adult patients with relapsed or refractory advanced renal cell carcinoma (RCC)
6	Dexmethylphenidate and Serdexmethylphenidate (Capsule)	Central nervous system (CNS) stimulant	March 2, 2021	Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older
7	Fosdenopterin (Injection)	Cyclic pyranopterin monophosphate (cPMP) substrate	February 26, 2021	Replacement therapy for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A
8	Melphalan flufenamide (Injection)	Anticancer peptide-drug conjugate	February 26, 2021	In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma
9	Casimersen (Injection)	Phosphorodiamidate morpholino oligomer	February 25, 2021	Duchenne muscular dystrophy (DMD) who have genetic mutations that are amenable to skipping exon 45 of the Duchenne gene

Source: https://www.drugs.com/newdrugs.html

DASIGLUCAGON

After the approval of nasal glucagon in 2019, new analogue dasiglucagon has been approved by FDA recently (March 22, 2021). Dasiglucagon, previously ZP4207, is a novel analogue of glucagon that is stable in aqueous formulation and does not need reconstitution. In a dasiglucagon molecule, 7 out of 29 amino acids are substituted to obtain a formulation stable in liquid form.

Mechanism of action

It is a glucagon receptor agonist. It increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for dasiglucagon to produce an antihypoglycemic effect.

Dasiglucagon has demonstrated established solubility and stability in an aqueous formulation. Pharmacokinetic studies have shown dasiglucagon to exhibit higher absorption and a longer plasma elimination half-life than traditional reconstituted glucagon. Pharmacodynamic studies have shown that a full dose of 0.6 mg dasiglucagon could efficiently raise blood glucose level (BGL) by ≥20 mg/dL (9–10 min) from baseline following insulin-induced severe hypoglycemia in patients with type 1 diabetes, as well as rapidly increase BGL with small doses under euglycaemic and hypoglycemic conditions.

Dosage forms & strengths

Injection, solution

- 0.6mg/0.6mL single-dose autoinjector or prefilled syringe
- 0.6 mg SC; if no response after 15 minutes, an additional 0.6-mg dose from a new device may be administered.

Storage: The product has a shelf-life of 36 months at refrigerated at 2-8ºC (36-46ºF) temperatures and is stable for up to 12 months at room temperature of 20-25ºC (68-77ºF).

Adverse Effects

>10%

- Adults: Nausea (57%), Vomiting (25%), Headache (11%)
- Children aged 12-17 yr: Nausea (92%), Vomiting (67%) Headache (17%)
- Children aged 6-11 yr: Nausea (25%), Vomiting (25%)

1-10%

- Adults: Diarrhea (5%), Injection site pain (2%)
- Children aged 12-17 yr: Injection site pain (8%)

Frequency Not Defined: Hypertension, Hypotension, Bradycardia, Presyncope, Palpitations, Orthostatic intolerance

Contraindications

1. Pheochromocytoma
2. Insulinoma

Drug interactions

- Beta-blockers
  - » Use with caution
  - » Beta-blockers may cause transient increases in pulse and blood pressure
- Indomethacin
  - » Use with caution
  - » When used with indomethacin, glucagon may lose its ability to raise blood glucose or may even produce hypoglycemia
- Warfarin
  - » Use with caution
  - » Glucagon may increase anticoagulant effect of warfarin

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Patient related services provided by Department of Pharmacology College of Medicine, NAIHS

1. **Plasma cholinesterase estimation at SBH**
   For confirmation and assessing severity of organophosphate (OP) poisoning.
2. **Drug information services at College of Medicine.**
   Drug and therapeutics related questions are answered from the department.

   Email: pharmacology@naihs.edu.np, Phone: 01-4881259 Ext 129/168

KEY MESSAGES OF THE ISSUE

1. Various immunomodulating therapies are being investigated for treatment of severe COVID-19. The outcome data regarding the use of immunomodulating therapy in the treatment of COVID-19 and findings, although not conclusive, are suggestive of decreasing the mortality and reducing length of hospital stay especially in severe COVID-19. Among the widely available treatments, corticosteroid therapy has been found to reduce the risk of all-cause mortality and duration of mechanical ventilation compared with placebo. The use of corticosteroids is currently recommended only for the treatment of patients with severe COVID-19. Early administration of inhaled budesonide may reduce the need of urgent medical care and time to recovery after early COVID-19. As inhalational glucocorticoids are widely available and relatively safe, this intervention may prove to be a breakthrough in management of early COVID-19.
2. Treatment of enteric fever needs to be directed by culture and sensitivity report as far as possible because of increasing antimicrobial resistance in *Salmonella typhi*. High rates of fluoroquinolone resistance are now reported in South Asia. Cefixime and ceftriaxone are associated with higher rates of relapse in comparison to oral azithromycin. Resistance to all three agents is appearing. Meropenem is recommended in case of resistance to azithromycin.
3. Statin-Associated Muscle Symptoms (SAMSs) are by far the most prevalent and important adverse effects of statins. Incidence of new-onset type 2 diabetes mellitus with statin treatment appears to be more common in patients with preexisting risk factors. Neurological conditions that have been associated with statin use include hemorrhagic stroke, cognitive decline, peripheral neuropathy, depression, confusion/ memory loss and aggression, and personality changes. Other statin-mediated adverse events include cataracts, gastrointestinal effects, urogenital health effects, gynecomastia, and reproductive effects.
4. The influence of dietary substances on drug effects depends on numerous variables ranging from physicochemical properties of the drug to host factors such as enzymes and transporters in the gastrointestinal (GI) tract as well as in the entire body. The physicochemical properties of food products may cause changes in the pharmacokinetics of drugs that may alter absorption of drugs. Some significant interactions that need attention

include that with warfarin, ACE inhibitors, tetracyclines and fluoroquinolones.

5. The topical use of honey for wounds and burn care meets most of the features of an ideal preparation for such use. Studies have shown no development of bacterial resistance and no emergence of mutants resistant to honey. There was no loss of bacterial sensitivity to honey over time and no appearance of bacteria resistant mutants. Preclinical research and clinical studies have shown the efficacy of honey in superficial and partial thickness burns therapy, when compared to other dressing products, making it a viable option as a valuable topical agent in clinical practice.

6. The pharmaceutical products should be stored under the conditions that prevent contamination and possible deterioration. The storage condition is important as they may impact the quality of the product. High temperature and relative humidity (RH) are the most important factors involved in drug degradation and other factors such as air quality, time and production process characteristics can also have significant impact on the final quality of the product.

7. Curcumin (constituent of turmeric) has several pharmacological effects such as antioxidant, anticancer, antibacterial, antiviral, and antidiabetic effects as well as anti-inflammatory activity. Other prominent beneficial effects of turmeric include antiapoptotic, antifibrotic, antiemetic, antinociceptive, antipyretic and bronchodilator effects. Broad-spectrum antiviral activity and immunomodulatory activity provides a strong rationale for testing curcumin for COVID-19 treatment. Low bioavailability is the major obstacle in attaining the therapeutic potential of oral curcumin. Curcumin encapsulated nano-carriers such as liposomes, niosomes, lipid complexation, micro/nano-emulsions and polymeric nanoparticles. This nano-formulated curcumin could be delivered in dry powder, nebulizer, solution, nasal spray or gel and may provide effective option.

8. In last three months (Feb 25-Apr26), nine new drugs have been approved by US-FDA. They are: **casimersen (**Phosphorodiamidate morpholino oligomer, indication- Duchenne muscular dystrophy with specific genetic mutations) **melphalan flufenamide (**Anticancer peptide-drug conjugate, indication- adult patients with relapsed or refractory multiple myeloma), **fosdenopterin (**Cyclic pyranopterin monophosphate substrate, indication- molybdenum cofactor deficiency, Type A) **dexmethylphenidate and serdexmethylphenidate (**Central nervous system stimulants, indication- Attention Deficit Hyperactivity Disorder, in patients 6 years of age and older) **Tivozanib (**Vascular endothelial growth factor receptor tyrosine kinase inhibitor, indication Adult patients with relapsed or refractory advanced renal cell carcinoma) **oritavancin (**Lipoglycopeptide antibiotic as 2nd product, indication- Acute bacterial skin and skin structure infections caused by designated Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus*), **ponesimod (**Selective sphingosine-1-phosphate receptor 1 modulator, indication- adults with relapsing forms of multiple sclerosis) , **dasiglucagon (**Glucagon analog, indication- severe hypoglycemia) **idecabtagene vicleucel (**B-cell maturation antigen, indication- Adult patients with relapsed or refractory multiple myeloma)

Please send your comments and suggestions either on following address or via:

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