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Special Editorial

The Centenary of the Discovery of Insulin

In January 1922, biochemist James Bertram Collip was working at his bench in the wee hours of the night. Collip had been ordered to spend his evenings in the laboratory at the University of Toronto, Canada, because his wife, small daughter, new baby, and sister-in-law were all sick with influenza at home.[1] He was on sabbatical from the University of Alberta and working there. Collip had been absorbed with the subject of diabetes for six weeks. Diabetes, unlike the viral diseases of the time, was uncommon and resulted from a flaw in the body's metabolism, notably the pancreas' function.[2]

Insulin's isolation in 1921 and subsequent delivery to a 14-year-old child in a diabetic coma in Toronto in 1922 was a groundbreaking scientific and clinical success that forever changed diabetes care, and it's commemorated in this themed edition of The Lancet.[3] Despite the discoverers' philanthropic feelings that "insulin belongs to the world," the lack of access to insulin over the past 100 years reveals catastrophic policy and operational failures.[4]

Insulin's first 100 years were a technical success, but access was a disaster. Although the prevalence of type 1 diabetes is increasing worldwide, the burden of death remains disproportionately high in low- and middle-income nations (LMICs).[5] As the year 2021 marks the 100th anniversary of the discovery of insulin, we take a look back at how far we've come, the global burden of type 1 diabetes, and our understanding of the disease's pathophysiology and management techniques.[5] Despite significant progress, discrepancies in insulin formulation access and availability persist, as evidenced by differences in disease-related survival and morbidity trends. During the COVID-19 pandemic, some of these imbalances were exacerbated by health-system issues.[6]

Improved access to insulin and related critical technologies for improved type 1 diabetes management in LMICs is clear potential, especially as part of universal health coverage. For the appropriate diagnosis and management of type 1 diabetes, these advances will necessitate concerted action and investments in human resources, community participation, and education, as well as adequate healthcare financing. More research is needed in LMICs, particularly in Africa, to increase our understanding of the burden, risk factors, and management strategies for type 1 diabetes.[6]

When it comes to insulin, money is a huge stumbling block. Despite efforts such as the World Health Organization's prequalification of insulin, which aimed to encourage more insulin manufacturers and lower costs, and the inclusion of long-acting insulin analogues and their biosimilars on the WHO Essential Medicines List (human insulin has been on the list since 1977), insulin remains unaffordable for many people. The WHO Essential Medicines List (EML) expert committee's decision this year to form a working group on highly-priced essential medicines may help to solve this problem to some extent.[2,3]

The focus of research and development has been on gradually newer insulin analogues—some of which have uncertain evidence of enhanced effectiveness despite higher costs—and continuous glucose monitoring gear, which are out of reach for the vast majority of patients around the world.[4-6] Oral insulin delivery could be a breakthrough in the management of diabetes mellitus but it does not seem to be a reality in the near future.[7]

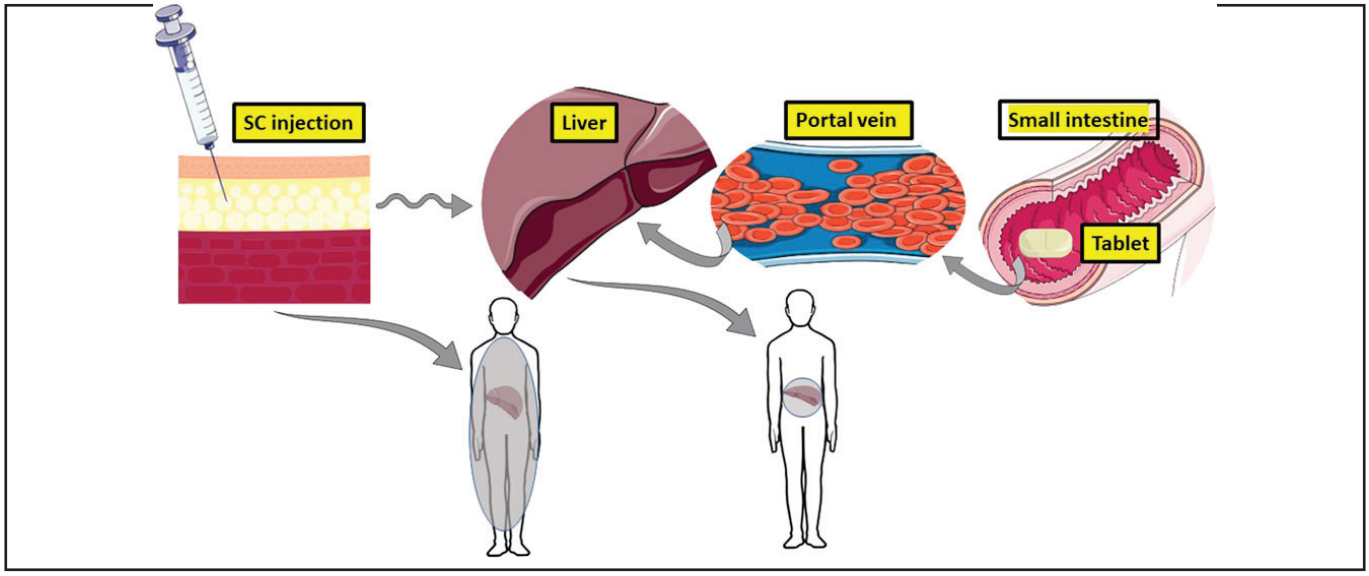

Figure 1: The theoretical advantage of oral insulin versus subcutaneous (SC) injection.[7]

As a result, nothing has changed in the treatment of type 1 diabetes patients in much of the world over the last century. In addition to having trouble accessing insulin, many patients lack access to basic blood glucose monitoring, diagnosis remains a challenge, and patient education is generally restricted.

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Nutraceuticals in Management of Osteoarthritis

Osteoarthritis (OA) is a degenerative disease characterized by articular cartilage and synovium inflammation that can cause swelling, stiffness, pain, and loss of mobility.[1] Current OA management is limited and largely confined to symptom management or total joint replacement if the joint function is severely compromised. There is a call for a shift towards helping OA patients to self-manage their condition.[3] Since diet is a factor that may affect OA, dietary and nutritional supplements are being looked for the management and prevention of OA.

Fish oil

The effectiveness and precise benefits of fish oil intake in patients with OA are still far from well understood. In fact, in vitro, and in vivo studies showed a dose-dependent decrease in induced inflammatory destruction of cartilage tissue associated with fish oil supplementation.[4] Proposed mechanisms for the anti-inflammatory actions of n-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from fish oil include competition with n-6 fatty acids; the EPA and DHA derived anti-inflammatory molecules called resolvins; the competition for receptors of n-3 products with proinflammatory molecules; the reduction in gene expression of cytokines, cyclo-oxygenase-2, and degrading proteinases; the interference in the signaling pathways of inflammation; and the reduction in lymphocyte proliferation.

Glycosaminoglycans (GAGs): Glucosamine, chondroitin sulfate, hyaluronic acid

GAGs are synthesized by chondrocytes and synoviocytes and are basic components of the extracellular matrix and synovial fluid. GAGs can also be introduced with food and their use as nutritional supplementation can be useful for OA prevention. From clinical and preclinical data, supplementation of glucosamine sulfate seems to improve joint function and reduce pain and also appears to stimulate cartilage regeneration, thus inducing regression of OA. In two randomized controlled trials, glucosamine sulfate, as well as chondroitin sulfate, mitigated the catabolic and degenerative

processes thanks to their anti-inflammatory and antioxidant properties. A pharmacokinetic study, however, suggests that the simultaneous ingestion of glucosamine and chondroitin sulfate has no synergic effect due to the competition between the two molecules in intestinal absorption. Additionally, hyaluronic acid has also been shown to improve the mechanical properties of the synovial fluid in vitro and has a biochemical regulatory role on joint tissues.[1]

Olive oil

The anti-inflammatory properties of olive oil are attributed to its phytochemicals, such as the phenolic compounds and monounsaturated fatty acids (MUFAs). In rats, it was demonstrated that an olive oil supplemented diet improves cartilage recovery after anterior cruciate ligament transection.[5] However, the lack of clinical trials demonstrating the effect of olive oil supplementation with diet limits the recommendation of this compound.

Methionine

Methionine is an essential amino acid for humans since the human organism is not able to synthesize it and therefore it is taken with the diet. The active form of methionine is S-adenosylmethionine (SAMe) is a precursor of glutathione. SAMe has antioxidant properties and, in the joints, provides levels of glutathione peroxidase, an antioxidant enzyme. In addition,

SAMe inhibits enzymes that degrade the cartilage protecting its proteins and proteoglycans. Some researchers show that SAMe promotes anabolic processes of cartilage, thus having a regulatory function in cartilage regeneration.[1]

Vitamin D supplements

Vitamin D deficiency is associated with the development or progression of OA as Vitamin D has effects on calcium absorption in cartilage and bone metabolism. However, there have been conflicting reports as to whether vitamin D supplements can reduce OA pain. A meta-analysis of 4 RCTs with 1136 patents showed that vitamin D supplements significantly reduced WOMAC (Western Ontario and McMaster Arthritis Index) pain and loss of function but had no effect on WOMAC stiffness or tibial cartilage volume.[3] Most of the studies, however, reveal Vitamin D to have a beneficial effect on lowering OA pain. Additional long-term trials are required to further determine its clinical benefits.

Botanical extracts

Botanical extracts are a large variety of substances obtained from plants and used as additives in diet.[1]

- Avocado/ soy unsaponifiable (ASU) components: Sterol-rich hydrolyzed lipid extract fraction from avocado and soybean. ASU has anabolic and anti-inflammatory properties on chondrocytes. ASU also stimulates transforming growth factor production, collagen, and aggrecan synthesis.
- Curcumin: Extracted from turmeric; aromatic molecule with an anti-inflammatory effect that in vitro studies showed to inhibit the activity of COX-2 and 5-LOX enzyme, thus protecting chondrocytes from the negative effects of IL-1β
- Oleoresin: Obtained from *Boswellia serrata* tree. It is rich in boswellic acids which exhibit an anti-inflammatory effect by inhibiting leukotriene synthesis by inhibiting the 5-Lipoxygenase enzyme through a non-redox reaction.
- Bromelain: Extracted from immature fruits and stem of pineapple. It contains proteolytic enzymes that may have anti-inflammatory, analgesic, antithrombotic, and antifibrinolytic properties. Several clinical trials used bromelain in the treatment of knee OA, with mixed and uncertain results, so that it is difficult, at this time, to give some indications about its use in the treatment of OA and more rigorous clinical trials are necessary.
- Ginger: Anti-inflammatory and anti-rheumatic agent used in traditional medicine and it contain bioactive molecules such as gingerols and shogaols. In vitro, it has been shown that ginger extract suppressed TNF-α and inhibited COX-2-mediated synthesis of proinflammatory cytokines.

Conclusion

The management and treatment of OA is based on the use of anti-inflammatory agents and analgesics, surgical procedures, and rehabilitation to enable healthy body weight, lifestyle, and physical activity. However, nutritional intervention represents an ongoing strategy for managing and preventing OA as a complement to traditional clinical treatment. Nutritional interventions could regulate the balance between anabolic and catabolic processes in joint tissue, influencing immune response, redox balance, and free-radical scavenging, thus providing for structural precursors of synovial fluid and extracellular matrix of cartilage.

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Approved Monoclonal Antibodies for COVID-19

Monoclonal antibodies (mAbs) may be the final choice in health crises such as severe COVID-19 and antimicrobial resistance (AMR).[1] Immediate passive humoral immunotherapy with neutralizing monoclonal antibodies is a potential prophylactic and therapeutic option to prevent COVID-19–related hospitalization and death. Combinations of mAbs are recommended for those with mild to moderate COVID-19 cases who don't need oxygen and are at a high risk of developing severe disease.

Casirivimab and imdevimab

Casirivimab and imdevimab are mAbs that are specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells. Regeneron Pharmaceuticals produced a mAb cocktail therapy containing casirivimab and imdevimab (REGN-COV2), which bind to non-overlapping epitopes of the SARS-CoV-2 spike protein RBD and hence prevent virus interaction to the human ACE2 receptor. It was approved for EUA by the FDA on November 21, 2020. For the treatment of adults and children with mild to moderate COVID-19, as well as those who are at high risk of advancing to severe COVID-19, a single intravenous infusion dose of 1,200 mg for both mAbs is advised. [2,3]

The findings of Chen et al. were crucial in the Food and Drug Administration's decision to grant emergency use authorization to bamlanivimab and the casirivimab–imdevimab combination for adults and children over the age of 12 with mild or moderate COVID-19 and a high risk of severe disease. SARS-CoV-2 was measured with RT-PCR (Real time polymerase chain reaction) as a proxy for the extent of viral infection and possibly viral replication in several studies. The findings imply that mAbs can lower the viral load in the nasopharynx by acting as an antiviral agent. The impact of mAbs and other medications on viral load could be a crucial criterion for the development of early COVID-19 treatment options. Patients with continuously high nasopharyngeal RNA shedding on day 7 were more likely to be hospitalized in Chen et al study than those with lower levels (12 %vs. 0.9 %).

According to Weinreich DM et al., REGN-COV2 improved virus clearance, especially in individuals who had not yet established an endogenous immune response (i.e., serum antibody–negative) or who had a high viral load at baseline. Between the combined REGN-COV2 dose groups and the placebo group, a possible difference in the percentage of patients with medically attended visits was observed (difference, 3%; 95 percent CI, 16 to 9), and this effect was almost entirely driven by patients who were serum antibody–negative at baseline (difference, 9%; 95 percent CI, 29 to 11). REGN-COV2 was as safe as one would expect from a fully human antibody against an external target. During the observation period, there was a low rate of major adverse events that occurred or worsened, as well as infusion-related or hypersensitivity reactions.[4]

Etesevimab and bamlanivimab

Two such neutralizing monoclonal antibodies, bamlanivimab and etesevimab, were isolated from convalescent plasma obtained from patients with Covid-19 in the United States and China, respectively. Etesevimab 1400 mg plus bamlanivimab 700 mg are used as a single IV infusion. These potent neutralizing monoclonal antibodies target the surface spike glycoprotein of SARS-CoV-2 that mediates viral entry into host cells.[2]

In a study by Dougan M et al, a total of 1035 patients were randomly assigned to receive either a bamlanivimab–etesevimab infusion or a placebo infusion. On day 29, 11 of 518 patients (2.1%) in the bamlanivimab–etesevimab group had a COVID-19-related hospitalization or death from any cause, compared to 36 of 517 patients (7.0%) in the placebo group (absolute risk difference, 4.8 percentage points; 95%CI, 7.4 to 2.3; relative risk difference, 70%; P0.001). There were no deaths in the bamlanivimab–etesevimab group; however, there were ten deaths in the placebo group, nine of which were attributed to COVID-19.[5] Among high-risk ambulatory patients, bamlanivimab plus etesevimab led to a lower incidence of Covid-19–related hospitalization and death than did placebo and accelerated the decline in the SARS-CoV-2 viral load.

Sotrovimab

Sotrovimab is a pan-sarbecovirus monoclonal antibody designed to prevent the progression of COVID-19 disease in high-risk patients. The Phase 3 COMET-ICE trial provided the data that supported the EUA for sotrovimab (ClinicalTrials.gov Identifier NCT04545060). Outpatients with mild to moderate COVID-19 who were at high risk of progressing to severe disease and/or hospitalization were included in the COMET-ICE experiment. Sotrovimab 500 mg IV (n = 291) or placebo (n = 292) were given to a total of 583 subjects. The proportion of individuals who were hospitalized for 24 hours or died from any cause by Day 29 was the primary outcome.[6] Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm (P = 0.002), resulting in a 6 percent absolute reduction in hospitalizations or death associated with sotrovimab and an 85 percent relative reduction in hospitalizations or death in comparison to placebo[6]

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Article Summary: Molecular Basis of the Therapeutical Potential of Clove (*Syzygium aromaticum* L.) and Clues to its Anti-COVID-19 Utility. Molecules. 2021;26(7):1880

Introduction

Inflammatory cytokine storm together with immune system impairment is commonly observed in patients with severe COVID-19. Several research studies have highlighted the advantages of dual therapies with antiviral and anti-inflammatory benefits. Due to the urgent need for such a pharmacological treatment, drug repurposing and herbal medicines are two of the most considered anti-COVID-19 approaches.

Clove (Syzygiumaromaticum L.) in herbal medicine and its active constituents

Syzygium aromaticum L. (also known as *Eugenia caryophyllata L.*) is an evergreen tree with sanguine flowers belonging to the family Myrtaceae that grows in tropical climates and has been widely used in Ayurveda and Chinese traditional medicines for over 2000 years. Cloves have long been used in both traditional medicine and for culinary purposes and serve to produce an essential oil known since ancient times in food flavorings, traditional medicine, and perfume production. Even though cloves are mostly used as a nutritional spice for food in the Western world, in the past, they have constituted a remedy for a variety of health concerns, with the clove anesthetic (due to eugenol), stimulating, antimicrobial, antifungal, antiviral, and antiseptic properties having been known for centuries.

On the other hand, the clove essential oil finds applications in dental care, including the treatment of gum infections, burns, and respiratory and digestive disorders. The other reported remarkable properties include antiangiogenic, anticancer, antioxidant, anti-inflammatory, and antimutagenic activities.

The American Food and Drug Administration (FDA) agency has confirmed the safety of clove buds, clove oil, and some clove ingredients as a food supplement, while the WHO has established the acceptable daily uptake of cloves in humans at 2.5 mg/kg body weight.

The spice contains a good amount of minerals like magnesium, manganese, potassium, iron, and selenium. Among the others, potassium as an important electrolyte of the cell and body fluids has a key role in heart rate and blood pressure control, while manganese is used by the body as a cofactor for the antioxidant enzyme superoxide dismutase. Additionally, cloves are a good source of beta carotene vitamin B1, vitamin B6, vitamin C, vitamin K, riboflavin, and vitamin A, used by the body for maintaining healthy mucus membranes and skin.

Several research studies have been carried out to identify the main clove phytochemicals. Dried clove buds contain ~20% essential oil, which is rich in eugenol, accounting for 70–90%. The other main phytochemicals isolated from clove essential oil include eugenyl acetate, β-caryophyllene, and several sesquiterpenes including α-cubebene, α-copaene, and γ- and δ-cadinene. Crategolic acid, vanillin, gallotannic acid, methyl salicylate, eugeniin, rhamnetin, kaempferol, eugenitin, oleanolic acid, methyl amyl ketone, methyl salicylate, α- and β-humulene, benzaldehyde, chavicol, and β-ylangene are present in lesser amounts. In particular, eugenol and minor constituents like methyl salicylate and methyl amyl ketone are responsible for the characteristic pleasant aroma of cloves.

Clove in respiratory problems

Traditional medicine uses cloves as respiratory aids, and in particular, the spice is one of the ingredients of teas used in tropical Asia to facilitate expectoration. Moreover, an aromatherapy procedure consisting of breathing in the aroma released from hot clove tea is another common way to use cloves for respiratory disorders like coughs, colds, asthma, bronchitis, and sinusitis. Moreover, it is customary in Asia to chew cloves for treating soreness of the throat and inflammation of the pharynx. Chewing cloves after their thermal treatment is reported to bring relief from severe coughing. Clove oil acts as an expectorant for treating respiratory disorders, including colds, bronchitis, cough, asthma, and upper-respiratory conditions. In mixtures with honey, it helps in the case of chronic cough.

Anti-Inflammatory, immunostimulatory, and antithrombotic properties

From a molecular point of view, clove buds contain flavonoids like β-caryophyllene, kaempferol, and rhamnetin, which contribute to their anti-inflammatory properties. In experimental animal models, eugenol (at 200 and 400 mg/kg doses) was shown to reduce the volume of pleural exudates without changing the total count of blood leukocytes, which indicates the anti-inflammatory activity of this molecule. Eugenol is believed to regulate the cellular inflammatory cascades, including the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and ERK (extracellular-

signal-regulated kinase)/MAPK (mitogen-activated protein kinase) pathways, and the release of proinflammatory interleukins. In other studies, LPS (lipopolysaccharide)-induced lung inflammation was relieved by the treatment with both whole clove aqueous extract and eugenol through a reduction of TNF-α (tumor necrosis factor-alpha) and inhibition of NF-κB signaling, also with an improvement in the alveolar damage. Remarkably, clove aqueous extract showed protective effects on an animal model of pyelonephritis a kidney inflammation reported in COVID-19 patients.

In experimental studies on animal models, clove oil improved the total white blood cell count and enhanced the delayed-type hypersensitivity response. Noteworthy, a dose-dependent restoration of both humoral and cellular immune responses was observed in cyclophosphamide-immunosuppressed mice treated with clove essential oil.

Clove oil has been shown to inhibit the platelet aggregation induced by the platelet-activating factor, arachidonic acid, and collagen, with a higher activity observed in the first two systems than the latter. In vivo experiments carried out on rabbits showed that clove oil at 50–100 mg/kg doses afforded total protection against the platelet-activating factor and good (70%) protection against arachidonic acid-induced shock due to pulmonary platelet thrombosis. Clove oil also inhibited thromboxane-A2 and 12-hydroxyeicosatetraenoic acid production by human platelets treated with C-14 arachidonic acid. Antithrombotic and antiplatelet aggregation effects were also studied on clove extracts by ex vivo methods measuring the fibrinolytic activity and the inhibitory effect on thrombin-induced platelet aggregation. The extracts showed remarkable fibrinolytic activity and inhibitory effects on platelet aggregation, suggesting clove anti-atherosclerotic potential.

Antiviral properties

Eugenol (4-allyl-2-methoxyphen, being the major constituent of cloves, was investigated for its antiviral activity by several research groups. Eugenol showed antiviral activity against the HSV-1, HSV-2, and influenza A virus (IAV), being able to inhibit IAV replication. It was also found active as an inhibitor of the Ebola virus in vitro.

The traditional therapeutic use of clove in respiratory disorders and its activity against different types of viruses, alongside its anti-inflammatory, immunostimulatory, and antithrombotic properties, are all attractive features highlighting its potential in the fight against the COVID-19 disease.

Clove is one of the medicinal plants currently employed to prevent and control the SARS-CoV-2-associated disease, together with *Eucalyptus globulus*, *Cymbopogon citratus*, *Zingiber officinale*, and other plants endowed with the advantage of being inexpensive and abundantly available around the globe. A protocol for the prevention and treatment of COVID-19 using cloves showing beneficial effect for the treatment provided that was carried out in the early stages of the disease has been published. It included the preparation of a decoction in which cloves are boiled in water with other plant materials for 15 min. The released volatile active principles are then inhaled by patients for five minutes. The same protocol also included a drinkable decoction obtained with cloves and other plant materials. Cloves are mentioned as one of the most frequently used spices and herbs during the current COVID-19 pandemic in the areas under investigation, together with other plants like cinnamon, ginger, black pepper, garlic, neem, and basil. Cloves are also being used in Morocco for the prevention and treatment of COVID-19. From a molecular point of view, some computational studies recommended phytocompounds extracted from cloves as potent anti-COVID-19 drugs, and one of them, kaempferol, was shown in silico to bind the substrate-binding pocket of the main protease of SARS-CoV-2 with high affinity interacting with the active site residues such as Cys145 and His41 through hydrophobic interactions and hydrogen bonding, suggesting that natural compounds such as clove flavonoids could act as novel inhibitors of SARS-CoV-2. Molecular docking studies have also shown high affinities of clove compounds bicornin and biflorin for main protease, suggesting their potential inhibitory activity.

Conclusion

The therapeutic use of cloves in traditional medicine to treat respiratory ailments and its experimentally proven activity against different types of viruses, as well its anti-inflammatory, immunostimulatory, and antithrombotic properties, all concur to compose a picture of the potential importance of cloves and their phytochemical constituents in the fight against the COVID-19. Aside from the above-mentioned features, clove essential oil has shown remarkable antibacterial effects against the infections of immunosuppressed hospitalized patients, suggesting its utility to also prevent secondary bacterial infections in COVID-19 patients. Future clinical data on the activity of cloves and their constituents on COVID-19 patients and more molecular insights on the specific clove phytochemical interactions with SARS-CoV-2 protein targets are desirable to realize the effective therapeutic protocols and design new drugs based on clove phytochemicals with optimized characteristics.

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Medication Errors

The use of medicine has become increasingly complex in recent years. It is a major cause of preventable patient harm. Medication error is broadly defined as any error in the prescribing, dispensing, or administration of a drug and health-related items. It is an important cause of adverse outcomes and it may lead to failure in achieving the therapeutic goal. Medication errors can be minimized with coordinated efforts of all the health care professionals including doctors, pharmacists, and nurses.

Types of Medication Errors

The major types of medication errors are prescribing, dispensing, and administration of drugs. The other errors may be monitoring errors, compliance errors, documentation errors, omission errors etc.

Prescription errors

According to Nepal Medical and Pharmacy Council act prescriptions are to be written by the authorized prescribers. A clinically significant prescribing error occurs as a result of a prescribing decision or prescription writing process.

Contributing factors for prescription errors

These include lack of adequate training, calculation errors (may be related to availability of different drug formulations), use of verbal orders, unidentified drug allergy, a formulation with irrational combination of drugs, out-of-list abbreviations, illegible handwriting, inappropriate use of decimal points, polypharmacy, and inability to get information on drug interactions.

How to minimize prescription errors

Prescription errors can be minimized by ensuring use of up-to-date reference sources, use of hospital management information system (HMIS), and ensuring proper history taking which includes medication history. Medication history helps to identify drug allergy as well as avoiding drugs that can have harmful interactions with drugs being taken.

Dispensing errors

This error may occur at any stage during the dispensing process which may start during the process of prescription handling to the supply of a dispensed product to the patient. Potential dispensing errors include wrong dose, wrong drug, or wrong patients.

Contributing factors for dispensing errors

Major contributing factors are: look alike and sound alike drug and dispensing environment. The dispensing environment with a lot of distraction and interruption also plays a vital role in dispensing error. Lack of knowledge about new medicines, use of outdated and/or incorrect references, poor dispensing procedures with inadequate checking, dispensing unfamiliar products with inaccurate knowledge, use of computerized labeling transposition and typing errors (a most common cause of dispensing error) and using acronyms for drugs e.g., ASA (aspirin), 6MP (6-mercaptopurine), PCM (paracetamol) are among the contributing factors for dispensing errors.

Measures to minimize dispensing error

These contributing factors can be minimized by ensuring a safe dispensing procedure, using different brands or separating look alike and sound alike products, focusing on the task at hand, keeping distraction/ interruptions to a minimum as far as possible, being aware of high-risk drugs e.g. Hypertonic electrolytes (Potassium chloride, Calcium chloride, and Magnesium sulfate), cytotoxic agent, IV insulin, and introducing good housekeeping practices.

Administration errors

Such type of error occurs between the drug received by the patient and the drug therapy intended to administer to the patient. It involves wrong patient, wrong route of administration, wrong drug, wrong dose, wrong dosage form, administration of an expired drug, and wrong time, etc.

Contributing factors for administration errors

Major factors are: failure to check the patients' identity before administration, storage of look-alike preparations side by side in the drug trolley, environmental factors such as noise, interruptions, and poor lighting while undertaking the drug round and dose calculation error

Methods to minimize administration errors

Administration errors can be minimized by checking patients' identity, keeping the prescription, the drugs and the patient in the same place so they can be checked against one another, ensuring the correct medication time and minimizing interruptions during drug rounds.

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Chronopharmacology and Clinical Applications

Introduction

Chronopharmacology refers to the study of biological rhythm dependencies of drugs to optimize drug therapy by selecting the appropriate time of drug administration, which is associated with maximum efficacy and minimal adverse effects. Rhythmic variations in various physiological, biochemical, and behavioral parameters occur in all living organisms including humans. These variations optimize energy usage by prioritizing certain body functions at certain times of the day and conserving energy at other times. Circadian rhythm, in which the cycle length is about 24 h, regulates many functions in humans.[1]

Circadian biorhythms are ubiquitous phenomena that recur daily in a self-sustaining, entrainable, and oscillatory manner in most organisms. Circadian rhythms orchestrate a wide array of complex physiological processes at all levels from molecular interactions and expression to phenotypic and behavioral responses. These biological rhythms synchronize endogenous, genetically based circadian 'clock' or 'pacemaker' mechanisms with changes in environmental cues (e.g. light-dark cycles) thus enabling the organism to adapt, anticipate, and respond to changes and maintain homeostatic periodicity in body functions. Numerous physiological processes and parameters such as core body temperature, sleep-wake cycles, cardiovascular function, feeding, endocrine secretions (e.g. melatonin, cortisol, growth hormone, prolactin), hepatic metabolism, renal function, and several others exhibit rhythmicity. Diverse rhythmic patterns of circadian gene expression occur in virtually every cell, tissue, and organ system in the body, and nearly half of the mammalian protein-coding genome is expressed with a circadian rhythm with tissue specificity. Biorhythms in gene regulation, biochemical processes, and physiological functions bear important implications in health, disease, and pharmacotherapy. Both basic and clinical studies have demonstrated that disruption of circadian rhythms can be either the cause or the effect of disease including metabolic syndrome, inflammation, and cancer. Furthermore, increased severity in some disease symptoms and 'flares' (e.g.asthma, rheumatoid arthritis) or acute events (e.g. myocardial infarction) can present at specific times of the day. These observations provide daily 'windows of opportunity to effectively align treatments with disease symptoms. [2]

Chronopharmacology (or chronomedicine) aims to incorporate knowledge of circadian (and/or other) biological rhythms to improve pharmacotherapy using two broad approaches: (1) direct targeting and modulation of the molecular clock (e.g. light therapy, melatonin administration), or (2) understanding and exploiting the rhythmic physiology and downstream outputs of the internal clock. To maximize therapeutic benefit and/or lower adverse effects, such approaches aim to recommend an optimal time for drug administration in populations with well-synchronized circadian physiology, especially for new and existing drugs with narrow therapeutic indices.[2]

Chronopharmacokinetics

Absorption: Both nutrient and drug transporters in the GI tract show circadian rhythms. For instance, the intestinal absorption of lipids shows a circadian rhythm, where the rate of absorption peaks during the active period of the organism. Consistently, circadian patterns of absorption occur for some commonly used lipophilic drugs (e.g. cyclosporine, tacrolimus, and propranolol), with greater absorption occurring during the day than at night. Circadian differences in the absorption of NSAIDs have been documented in humans. The increased rate of absorption may be explained by daily variations in the gastric transit time and/or in intestinal blood flow.[2]

Distribution: Diurnal variations in both cardiac output and fractional blood flow rates to organs (e.g. brain, liver, skin, muscle) have been documented in both animals and humans. Both cardiac output and organ flow rates tend to be higher during periods of activity. Therefore, for small molecule drugs with high diffusion rates, their transport out of capillaries can be limited by circadian variations in cardiac output and blood flow rates to different organs. It is well documented that various ion channels, transporters, and efflux pumps show circadian variations in tissue expression, which can potentially impact the transport and efflux of drug substrates in a tissue-specific manner. Protein binding in both plasma and tissue is another major determinant of drug distribution. Indeed, albumin and other specific plasma binding proteins (e.g. transcortin and sex-hormone binding globulin) show circadian variations in the systemic circulation, which can alter the plasma-free fraction of highly bound drugs, and consequently impact their distribution.[2]

Metabolism: The optimization of metabolism and energy expenditure are key tasks of the circadian timing system. Importantly, fasting-feeding cycles accompanying rest-activity rhythms are major timing cues that synchronize rhythmic processes in the body. Within this context, the evolution of a time-dependent mechanism for the detoxification of noxious components ingested during food consumption is particularly relevant in mammals. Thus, it can be reconciled that the same underlying xenobiotic detoxification system plays an important role in the timing of drug metabolism, manifesting itself in circadian pharmacokinetics and pharmacodynamics, hence producing circadian changes in drug efficacy and toxicity.[2]

Although circadian variations are observed in nearly all factors controlling hepatic metabolism, the relative contribution to the circadian metabolism of a drug can vary. Numerous cytochrome P450 genes in the liver show circadian rhythmicity in expression. Enzymes involved in phase two metabolism including glutathione S-transferase, carboxylesterase, cysteine dioxygenase, UDP glucuronosyltransferase, and sulfotransferase are also expressed in a circadian manner. Rapid advances in molecular biology techniques [e.g., molecular cloning, gene editing, and chromatin immunoprecipitation (ChIP) analysis] have revealed both direct and indirect

mechanisms of core clock gene regulation of circadian drug-metabolizing enzyme transcription.[2]

Excretion: For most drugs, this process is primarily mediated by the kidney whereas biliary excretion and subsequent fecal elimination occur with some drugs. The circadian presence of efflux pumps in the bile canalicular membranes may influence the excretion of certain types of drugs from the hepatocytes into bile. Circadian rhythms have been documented in all three contributory processes of kidney excretion—glomerular filtration, tubular secretion, and tubular reabsorption. Studies evaluating daily glomerular filtration rate (GFR) using inulin as a marker suggest that GFR shows a circadian variation that peaks during the daytime in humans and is lower at night. For drugs that are primarily eliminated through glomerular filtration and show very low protein binding, their circadian variation in renal clearance would depend primarily on daily GFR fluctuation. For example, the circadian variation of renal excretion of amikacin, an aminoglycoside antibiotic, shows a pattern like that of GFR. Consistently, the antibiotic gentamycin displayed the best renal tolerability following afternoon dosing instead of dosing during the rest period (midnight to 7:30 AM) in patients with severe infections. However, for highly bound drugs, circadian variation in plasma protein binding can also affect circadian changes in renal excretion.[2]Similar to other tissues, the kidney also possesses an intrinsic circadian timing system with clock-controlled tissue-specific output genes. Many output genes are involved in the control of sodium ions, water balance, and nutrient/xenobiotic transport. Specific transporters in the kidney proximal tubule including P-glycoprotein, various organic acid and base transporters, and proteins of the solute carrier families, which are involved in the tubular secretion of drugs display circadian rhythms. Ampicillin, a drug primarily excreted by tubular secretion shows circadian variation in clearance, which indicates a possible circadian rhythm in the tubular secretion process. These findings point to a central role of core circadian clock function in renal physiology and pharmacology. Both the urinary pH and urinary flow rate display diurnal rhythms, with urinary pH being more acidic during the inactive period and urinary flow rate peaking during the active period.[2]

Chronopharmacodynamics

Drug activity is modulated by the circadian rhythms of 1) its direct intracellular target and triggered pathways and 2) the extracellular environment circadian status as a result of the control by the Circadian Timing System (CTS) of most physiologic functions, including the cardiovascular, immune and inflammatory, energy regulation, and nervous systems.[3] Studies have revealed significant differences in drug effects with different timing of dosing, despite showing the same concentration-time profiles in plasma and/or at their site(s) of action. Rhythmic changes in free-to-bound drug, target or receptor availability, downstream mediators, and activity levels of rate-limiting steps in pharmacologic signaling pathways in drug-targeted tissues are some factors that can produce pharmacodynamic effects of varying intensities based on dosing time. This phenomenon is particularly well-documented for diverse anticancer agents.[2]

Clinical relevance of chronopharmacology

Several Phase III clinical trials testing chronotherapy versus conventional non–time-stipulated treatment schedules have resulted in up to fivefold better tolerability and anear doubling in efficacy. Meta-analyses of chronotherapy schedules have further suggested a survival benefit. Pioneering studies have highlighted the relevance of morning dosing of glucocorticoids to minimize adverse events, resulting from adrenal suppression, resulting in the current timing recommendations for glucocorticoid intake in daily medical practice. Evening dosing has been recommended for most theophylline preparations to enhance bronchodilation and reduce side effects in asthmatic patients. However, morning dosing was shown to be more effective and safer for a sustained-release preparation of theophylline. Similarly, evening dosing has been recommended for several anti- H1 and anti-H2 antihistamines in allergic and gastritis subjects, respectively, as being both more effective and better tolerated. Clinical studies have also revealed the relevance of circadian rhythms for anticoagulant therapy in patients with thromboembolic disorders, while emphasizing the occurrence of rhythmic and nonrhythmic patients regarding heparin chronopharmacology.[3]

Technology for circadian drug delivery

Clinical chronotherapeutics has motivated both the development of programmable-in-time drug delivery pumps and the design of new drug formulations aiming at targeting specific circadian time windows. These recent technologies, together with the development of forecasting methods, are an important prerequisite for successfully translating the results of theoretical approaches into the clinics.[3]

Programmable-in-time infusion pumps

Conventional infusion protocols of cancer chemotherapy only consider drug doses, duration, and frequency of infusions. As a result, treatment times often vary among and within patients, yet mostly between 9:00 and 17:00, that is, over only one-third of the day span, for hospital logistics reasons. In contrast, circadian chronomodulated schedules stipulate the time courses and parameters of the delivery profile for each anticancer medication over the 24-hour period to achieve the best therapeutic index, according to biologic rhythm-based specifications. This includes times of onset and offset of infusion and variation of flow rate, ranging from constant to sinusoidal or gradually increasing or decreasing. These new concepts of drug delivery have triggered the industrial development of non-implantable multichannel programmable-in-time pumps, which in turn have fostered the clinical development of cancer-chronotherapeutics. Multiple circadian infusion schedules are then jointly administered to non-hospitalized patients, with minimal or no medical or nursing intervention. The advent of the IntelliJect device with

four 30-ml reservoirs enabled the development of the first combination schedule of 5-fluorouracil (5-FU)– leucovorin–oxaliplatin and led to the initial demonstration of the safety and efficacy of this three-drug chemotherapy given according to a circadian-chronomodulated delivery schedule. Melodie, a second generation of electronically engineered four-channel programmable pumps, represented considerable technological progress, through increased energy autonomy, flexible reservoir capacity, rapid programming of any delivery schedule, computer storage of treatment protocols and patient data, as well as actual drug delivery reports for each treatment course. The infusion pressure of this pump allowed the safe and effective administration of irinotecan–5-FU–oxaliplatin in a European trial involving conventional or chronomodulated three-drug infusions into the hepatic artery. This device is currently being upgraded to become the first connected e-chronopump. Further applications are foreseen for chronic antibiotic or nutrition delivery, among others.[3]

Modified release of oral drugs

Chronotherapeutics concepts have further elicited the development of cutting-edge technologies for modified release (MR) drug formulations aiming at selective tissue exposure at the desired time window over the 24 hours. For instance, the physiologic nocturnal high values of plasma melatonin were mimicked with circadin, a melatonin formulation that releases this hormone over 5–7 hours following evening intake. Similarly, a MR formulation of prednisone was developed to achieve sustained low-dose tissue exposure during the early night span, following evening intake, and a rise in plasma levels starting near 4:00, to culminate around 8:00, and decreased gradually thereafter, thus mimicking the physiologic circadian pattern of cortisol secretion. Such chronomodulated release of prednisone would further counteract the proinflammatory cytokines that are usually released at night, and contribute to the early morning joint inflammation that characterizes rheumatoid arthritis. Indeed, MR prednisone decreased by 20% disease symptoms compared with placebo when associated to standard anti-rheumatic drugs and achieved a better reduction of morning stiffness compared with immediate-release prednisone. Other drug formulations aim at achieving a delayed peak exposure in the early morning when the drug is administered before going to bed to prevent acute events in the early morning. For instance, controlled pulsatile release capsules of montelukast sodium were developed for the prevention of episodic attack of asthma in the early morning and associated allergic rhinitis. It is also possible to combine several active compounds in the same formulation to insure specific delays in between each drug exposure. For instance, a multilayered multidisc tablet comprising two agents enveloped by drug-free barrier layers was developed in the context of chronotherapeutic disorders, employing two model drugs, theophylline and diltiazem, and provided two pulses of drug release. Apart from oral administration, transdermal technologies have been developed to achieve proper drug release timing according to skin temperature. This formulation has the advantage to adapt to the individual patient's temperature rhythms allowing personalized drug timing.[3]

Toward rhythm-sensing drug-releasing nanoparticles

Inter- and intrapatient variability critically impact on the tolerability and efficacy of drugs given at their recommended dose level. For instance, systemic drug exposure can vary more than 10-fold in individual patients, despite dose adjustment to body weight or surface area. Such variability greatly limits the success rate of pharmacotherapies. Although chronomodulated delivery at fixed time appeared to reduce such intersubject variability in maximum plasma drug levels, as shown for 5-FUand oxaliplatin it did not eliminate CTS differences among subjects, resulting in important differences in drug elimination kinetics. Novel nanotechnology-based approaches could link drug release to a relevant molecular circadian rhythm in the cells of interest. This would achieve effective delivery of chronotherapy according to individual patient rhythms independently from drug timing. Rhythmic trigger-elicited drug formulation could present a great benefit particularly in the field of cancer research, as anticancer chemotherapy commonly results in dose-limiting adverse events, thus favoring acquired resistance, poor efficacy, and poor patient outcomes.[3]

Conclusion

Chronopharmacotherpeutic strategies in optimizing the timing of drug administration have been implemented in various diseases exhibiting circadian variations. Innovative chronopharmacological drug delivery systems have also been developed to circumvent the need for administering the drugs at odd timings. However, interindividual variations, interspecies variations, high cost of drug trials incorporating chronopharmacological approaches, and absence of a reliable chronobiological biomarker to guide chronopharmacotherapy are major limitations in this field and warrant further research.

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List of Recently Approved Drugs by US Food and Drug Administration (USFDA)

S.N.	Drug	Group/Class	Date of Approval	Indications
1	Belzutifan	Selective inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α)	August 13, 2021	Treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery
2	Difelikefalin	Selective peripheral kappa opioid receptor agonist	August 23, 2021	Treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (HD)
3	Lonapegsomatropin-tcgd	Human growth hormone	August 25, 2021	Once-weekly for the treatment of pediatric growth hormone deficiency
4	Mobocertinib	Oral tyrosine kinase inhibitor	September 15, 2021	Treatment of patients with epidermal growth factor receptor (EGFR) exon20 insertion mutation-positive metastatic non-small cell lung cancer (mNSCLC)
5	Ranibizumab-nuna (intravitreal)	Vascular endothelial growth factor (VEGF) inhibitor	September 17, 2021	Treatment of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), and myopic choroidal neovascularization (mCNV)
6	Ruxolitinib	Topical Janus kinase (JAK) inhibitor	September 21, 2021	Treatment of atopic dermatitis
7	Atogepant	Oral, calcitonin gene-related peptide (CGRP) receptor antagonist	September 28, 2021	Preventive treatment of episodic migraine in adults
8	Maralixibat	Ileal bile acid transporter (IBAT) inhibitor	September 29, 2021	Treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older.
9	Avacopan	Complement 5a receptor (C5aR) antagonist	October 7, 2021	Adjunctive treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis
10	Asciminib	Tyrosine kinase inhibitor	October 29, 2021	Treatment of patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML)

Source: https://www.drugs.com/newdrugs-archive/november-2021.html

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. Osteoarthritis (OA) is a degenerative disease characterized by articular cartilage and synovium inflammation that can cause swelling, stiffness, pain and loss of mobility and is one of the most significant causes of disability in the world. As OA management currently is confined to conventional approaches targeting symptom relief, there is call for a shift towards helping OA patients to self-manage their condition and dietary supplements are

being explored for this purpose. Nutraceuticals refer to compounds or materials that can function as nutritional supplements and exert a potential therapeutic effect, including the relief of pain in OA and as well help in regeneration capacities of the joint cartilage. Some of the dietary and nutritional supplements that have been found beneficial in prevention and management of OA are: fish oil, glycosaminoglycans, olive oil, methionine, Vitamin D supplements, botanical extracts.

2.. The US-FDA has granted Emergency Use Authorizations (EUAs) to three anti-SARS-CoV-2 monoclonal antibody (mAb) products- bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab, for the treatment of mild to moderate COVID-19 in non-hospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk of developing severe disease and/or requiring hospitalization.

3. Clove has experimentally proven activity against different types of viruses in addition to anti-inflammatory, immunostimulatory, and antithrombotic properties pointing to the potential importance of its phytochemical constituents in the fight against the COVID-19. Clove essential oil has also been shown to have remarkable antibacterial effects against the infections of immunosuppressed hospitalized patients, suggesting its utility to prevent secondary bacterial infections. Future clinical data on the activity of cloves and their constituents on COVID-19 patients and more molecular insights on the specific clove phytochemical interactions with SARS-CoV-2 protein targets will be useful in developing effective therapeutic protocols and design new drugs based on clove phytochemicals with optimized characteristics.

4. Medicines are used for the benefit of the patient but medication errors may contribute to the harmful effects for the patient. Following standard steps and being systematic in prescription writing, dispensing and administration of drugs can decrease the incidence of medication errors and give maximum benefit of the medicines to the patient.

5. Circadian biorhythms are ubiquitous phenomena that recur daily in a self-sustaining, entrainable, and oscillatory manner. Chronopharmacology aims to incorporate knowledge of circadian (and/or other) biological rhythms to improve pharmacotherapy. Chronopharmacotherpeutic strategies in optimizing the timing of drug administration have been implemented in various diseases exhibiting circadian variations. Innovative chronopharmacological drug delivery systems have also been developed to circumvent the need for administering the drugs at odd timings. However, interindividual variations, interspecies variations, high cost of drug trials incorporating chronopharmacological approaches, and absence of a reliable chronobiological biomarker to guide chronopharmacotherapy are major limitations in this field and warrant further research.

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