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Editorial

Reducing irrational use of drugs has been a challenge to medical fraternity. Irrational use of drugs results in various unwanted effects that include the adverse drug reactions that may lead to serious consequences and abuse of resource. "Abstracts in Focus", a new section is started from the first issue of second volume focuses on some of the very commonly used drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) and gastric acid suppressants (proton pump inhibitors and H2 receptor blockers) have been used very widely and frequently without considering the risks and are focused on this issue. We hope the abstracts and the material included in this issue will serve the purpose of promotion of rational use of medicines.

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Guideline for Treatment of Uncomplicated Malaria in Nepal

The human *Plasmodium* species transmitted from person to person are *P. falciparum, P. vivax, P. ovale* and *P. malariae.* Increasingly, human infections with the monkey malaria parasite *P. knowlesi* are being reported from the forested regions of South-East Asia and particularly the island of Borneo. *P. vivax* is the most important causative agent of human malaria in Nepal. About 90-95% of malaria cases are due to *P. vivax* and rest due to *P. falciparum, P. vivax* and *P. ovale* forms hypnozoites, which are dormant parasite stages in the liver that cause relapses of infection weeks to years after the primary infection. Thus, a single mosquito inoculation may result in repeated bouts of illness.

Treatment of uncomplicated *P.vivax, P.ovale, P.malariae or P.knowlesi* malaria

The objective of treating *P. vivax/P. ovale* malaria is to effectively cure both blood-stage and liver-stage infections (radical cure), thereby preventing recrudescence and relapse, respectively. *P. malariae and P. knowlesi* only causes blood stage infection. On the Indian subcontinent where most of the world's *P. vivax* malaria occurs, the parasites are mainly sensitive to chloroquine. A travel history specifically to determine possible infections acquired outside the Indian subcontinent should always be obtained, as this will guide the choice of treatment.

First-line treatment

The first-line treatment for *P.vivax, P.ovale,P.malariae or P.knowlesi* is chloroquine (CQ) for 3 days.

Day 1: chloroquine is given at an initial dose of 10 mg base/ kg body weight.

Day 2: 10 mg/kg body weight.

Day 3: 5 mg/kg body weight.

When the weight of the patient cannot be determined, dose for chloroquine can be calculated based on age based band as shown in Table 1.

Second-line treatment

The recommended second-line option in Nepal is dihydroartemisinin + piperaquine (DHA/PPQ). The longer half-life of piperaquine gives it an advantage over lumefantrine in the treatment of vivax malaria. It is programmatically most suitable to have the same medicines as second-line for both vivax and facilparum malaria. So, DHA/PPQ is also the second-line ACT for P. falciparum in Nepal.

DHA/PPQ (40mg/320mg) is given over 3 days: dihydroartemisinin at a dose of 4 mg/kg bw per day and 18 mg/kg bw per day piperaquine once a day for 3 days

Table 1: Dosing of chloroquine based on age based bands.

Days	Medicine	AGE(years)				
		< 1 year	1-4	5-9	10-14	>14
1	Chloroquine tablet (150 mg)	½	1	2	3	4
2	Chloroquine tablet (150 mg)	½	1	2	3	4
3	Chloroquine tablet (150 mg)	½	½	1	1½	2
Total		**1½**	**2½**	**5**	**7½**	**10**

Situations when second line antimalarial (DHA/PPQ) should be used:

- When a patient does not tolerate or has adverse reactions to the first-line medicine.
- Recrudescence (treatment failure) - reappearance of symptoms and parasites within 28 days following initial antimalarial treatment of the first- line drug.
- Suspected chloroquine-resistant vivax infection – all cases imported from areas with chloroquine-resistant infections (Mekong Region, Countries in South America and Africa, Indonesia, Timor-Leste and Papua New Guinea) should be considered as potentially CQ resistant and treated with the second-line medicine.

Table 2: Dosing of DHA/PPQ based on age and body weight

Weight (Kg)	Age (Years)	Dihydroartemisinin(DHA)/ Piperaquine (PPQ) 40mg/320 mg base tablets		
		Day 1	Day 2	Day 3
<10	Under 1	¼ tab	¼ tab	¼ tab
11-24	1-6	1 tab	1 tab	1 tab
24-50	7-13	1½ tab	1½	1½
50-70	14-18	2 tabs	2 tabs	2 tabs
≥70	≥18	3 tabs	3 tabs	3 tabs

Anti-relapse (radical) treatment

To prevent relapse, *P. vivax* malaria should be treated in children and adults (except pregnant women, infants aged <6 months, and women breastfeeding infants <6 months) with a 14-day course of primaquine at 0.25 mg/kg body weight per day. When the weight of the patient can not be obtained, dose calculation for primaquine can be based on table 3. G6PD level should be done when available.

Treatment of *P. falciparum* malaria

The clinical objectives of treating uncomplicated falciparum malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. Cure is defined as elimination of the parasites from the body. The public health objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

First-line treatment

The first-line treatment for falciparum malaria is artemether + lumefantrine (AL) given over three days (Table 4) and a single dose primaquine.

Target dose range of artemether + lumefantrine (20mg+120mg in a tablet)): Total dose of

5-24 mg/kg - bw of artemether and 29-144 mg /kg- bw of lumefamtrine.

Table 3: Dosing of primaquine based on age

Days	Medicine	Age in Years					Follow-up schedule
		6 months <1*	1-4	5-9	10-14	>14	
1	Primaquine (7.5mg)	Nil	½	1	1½	2	
2	Primaquine (7.5mg)	Nil	½	1	1½	2	
3	Primaquine (7.5mg)	Nil	½	1	1½	2	✓
4-6	Primaquine (7.5mg)	Nil	½	1	1½	2	
7	Primaquine (7.5mg)	Nil	½	1	1½	2	✓
8-13	Primaquine (7.5mg)	Nil	½	1	1½	2	
14	Primaquine (7.5mg)	Nil	½	1	1½	2	✓
TOTAL TABLETS		Nil	3½	7	10½	14	

(* 2.5 mg tablet of primaquine should be given, 1 tab daily for 14 days in 6 months - 1 yr)

Table 4: Dosing of artmemether+lumefantrine and primaquine based on weight and age

Weight	Age (yrs)	Artemether+ Lumefantrine*						Primaquine (0.25 mg/kg)
		Day 1		Day 2		Day 3		
		First Dose	After 8hrs	AM	PM	AM	PM	
<15 kg	< 3	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	½ tablet (excluding breastfeeding infants less than 6 months of age
15-25 kg	3-9	2 tabs	2 tabs	2 tabs	2 tabs	2 tabs	2 tabs	1 tablet
25-35 kg	10-14	3 tabs	3 tabs	3 tabs	3 tabs	3 tabs	3 tabs	1.5 tablets
35kg and Above	≥14	4 tabs	4 tabs	4 tabs	4 tabs	4 tabs	4 tabs	2 tablets

* A tablet contains 20mg+120mg artemether and lumefantrine repectively

To reduce transmission – Primaquine single dose of 0.25 mg/kg bw (except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months). Testing for glucose-6- phosphate dehydrogenase (G6PD) is not required. For ease of monitoring and to ensure compliance, primaquine should be given on day 1 along with the first dose of AL as directly observed treatment.

Second-line treatment

The recommended second-line option is dihydroartemisinin + piperaquine (DHA/PPQ) as given above for treatment of uncomplicated *P.vivax, P.ovale, P.malariae or P.knowlesi* with added single dose primaquine.

Second-line antimalarial should be used in the following situations:

- Patients not tolerating or adverse reactions to the first line medicine.
- Recrudescence (treatment failure) - reappearance of symptoms and parasites within 28 days following initial antimalarial treatment of the first-line drug.

Mixed infection

Mixed malaria infection are common in endemic areas. In Nepal, mixed infection (mostly vivax and falciparum) constitute less than 1 percent of the total case burden. ACTs are effective against all malaria species and is the treatment of choice for blood stage mixed infection. In case of vivax or ovale mixed infection with P. falciparum, 14 days of primaquine should be given along with the first- line ACT (AL) for 3 days. Other mixed infections (*P. malariae or P. knowlesi*) should be treated like uncomplicated *P. falciparum* infection.

Recurrent malaria

Recurrence of malaria can result from re-infection or recrudescence (treatment failure), or relapse in the case of vivax or ovale malaria. Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual or substandard medicine. It is important to determine from the patient's history whether he or she vomited the previous treatment or did not complete a full course of treatment. Treatment failure must be confirmed parasitologically. This may require referring the patient to a facility with microscopy, as P. falciparum histidine-rich protein-2 (PfHRP2)-based RDT tests may remain positive for weeks after the initial infection even without recrudescence. To avoid missing treatment failures patients should always be asked whether they received antimalarial treatment within the preceding 1–2 months.

Treatment of uncomplicated malaria in pregnant women and lactating mothers

Vivax malaria should be treated with CQ as in non-pregnant women, however the use of primaquine to prevent relapse is contraindicated in pregnancy and lactating mothers. The treatment regimen for pregnant women and lactating mothers presenting with vivax malaria is as below:

– CQ (25mg/kg) over 3 days to cure the current blood-stage infection (as above), then

– CQ 300mg every week as chemoprophylaxis for the remaining duration of the pregnancy and until the breastfed baby is 6 months of age.

This is to prevent the development of clinical disease by hypnozoites released intermittently from the liver. Once the breastfed baby is older than 6 months of age, the mother should receive a 14 course of primaquine to ensure radical cure.

Falciparum malaria: Falciparum malaria during pregnancy carries a high mortality for the fetus and increased morbidity for the pregnant woman. Pregnant women in all trimesters and lactating mothers should be treated with the first-line ACT (AL) as in non-pregnant women.

Source: *National Malaria Treatment Protocol 2019. Epidemiology and Disease Control Division Department of Health Services Teku, Kathmandu (July 2019).*

Article Summary: Safety of Four SGLT2 Inhibitors in Three Chronic Diseases: A Meta-analysis of Large Randomized Trials of SGLT2 Inhibitors

Introduction

Large randomized trials of sodium-glucose transporter 2 (SGLT2) inhibitors have been conducted on the purpose of assessing the cardiorenal or death endpoints. However, those individual trials are underpowered to evaluate the specific endpoints relevant with safety. Although there have been meta-analysis studies published which have assessed the safety of SGLT2 inhibitors in type 2 diabetes (T2D), these studies have produced the inconsistent findings. Moreover, there is a lack of relevant meta-analyses that have assessed the safety of the sodium-glucose transporter 2 (SGLT2) inhibitors in different chronic diseases.

Methods

In this study the large randomized placebo-controlled trials of SGLT2 inhibitors that aimed at assessing cardiovascular or renal outcomes in patients with T2D, or in patients with chronic heart failure (CHF), or in patients with chronic kidney disease (CKD) were included. The eight safety outcomes of interest were fracture, diabetic ketoacidosis, amputation, urinary tract infection, genital infection, acute kidney injury, severe hypoglycemia, and volume depletion. We used a random-effects model to perform meta-analysis, to generate pooled risk ratios (RRs) and 95% confidence intervals (CIs). Heterogeneity was estimated by I^2. We performed subgroup analysis respectively stratified by different chronic diseases and different SGLT2 inhibitors, and tested the subgroup effects using Cochran's Q test. *P* value <0.05 means statistical significance.

Results

After literature search (search until September 25th, 2020) and study selectio, included eight large randomized trials of SGLT2 inhibitors were included : DAPA-CKD- assessing dapagliflozin in CKD patients, EMPEROR-Reduced- assessing empagliflozin in CHF patients, DAPA-HF assessing dapagliflozin in CHF patients, VERTIS CV-assessing ertugliflozin in T2D patients, CREDENCE- assessing canagliflozin in T2D patients, DECLARE–TIMI- assessing dapagliflozin in T2D patients, CANVAS Program- assessing canagliflozin in T2D patients, and EMPA-REG OUTCOME assessing empagliflozin in T2D patients. All the included studies had the low bias risk, and involved a total of 33,124 participants in the SGLT2 inhibitor group and 26,568 participants in the placebo group presents the original data used for meta-analysis.

Compared with placebo SGLT2 inhibitors significantly reduced the risk of acute kidney injury (RR 0.75, 95% CI 0.66–0.85; *p* for drug effect <0.001), while SGLT2 inhibitors showed a reduced trend in the risk of severe hypoglycemia (RR 0.86, 95% CI 0.71–1.03; *p* for drug effect = 0.096). On the contrary, SGLT2 inhibitors significantly increased the risks of diabetic ketoacidosis (RR 2.57, 95% CI 1.53–4.31; P for drug effect <0.001), genital infection (RR 3.75, 95% CI 3.00–4.67; P for drug effect <0.001), and volume depletion (RR 1.14, 95% CI 1.05–1.24; *p* for drug effect = 0.002); while SGLT2 inhibitors showed the increased trends in the risks of fracture (RR 1.07, 95% CI 0.99–1.16; P for drug effect = 0.081), amputation (RR 1.21, 95% CI 0.97–1.51; P for drug effect = 0.085), and urinary tract infection (RR 1.07, 95% CI 0.99–1.15; *p* for drug effect = 0.074). The results of subgroup analysis according to different diseases ($P_{subgroup}$ ranged from 0.205 to 0.773 and different SGLT2 inhibitors ($P_{subgroup}$ ranged from 0.054 to 0.757). Analysis of the results suggests that the effects of SGLT2 inhibitors on the eight safety outcomes assessed in the study were consistent across three chronic diseases (i.e. T2D, CHF, and CKD) and four SGLT2 inhibitors (i.e. dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin).

This study is the first one that evaluated the safety of four SGLT2 inhibitors (i.e. dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin) in three chronic diseases (i.e. T2D, CHF, and CKD), and has two key findings. First, SGLT2 inhibitors versus placebo significantly reduced the risk of acute kidney injury (RR 0.75) and showed a reduced trend in the risk of severe hypoglycemia, regardless of type of chronic diseases and type of SGLT2 inhibitors. Second, SGLT2 inhibitors versus placebo significantly increased the risks of diabetic ketoacidosis (RR 2.57), genital infection (RR 3.75), and volume depletion (RR 1.14), and showed increased trends in the risks of fracture, amputation, and urinary tract infection, regardless of type of chronic diseases and type of SGLT2 inhibitors. Compared with prior meta-analysis studies which assessed the safety of SGLT2 inhibitors only in T2D, our study included three recently published trials and therefore assessed the safety of different SGLT2 inhibitors in three chronic diseases.

One strength of this meta-analysis is that all the original studies included were of high quality. On the contrary, one weakness is that the studies included in the meta-analysis were conducted in patient populations with very considerable differences in their baseline characteristics, including the comorbidities. Thus, the findings identified by this meta-analysis need to be further verified in well-designed studies minimizing ascertainment bias.

Conclusion

SGLT2 inhibitors significantly reduce the risk of acute kidney injury, and show the reduced trend in the risk of severe hypoglycemia; whereas this drug class significantly increases the risks of diabetic ketoacidosis, genital infection, and volume depletion, and shows the increased trends in the risks of fracture, amputation, and urinary tract infection, regardless of type of underlying diseases and type of SGLT2 inhibitors. These findings will guide that specific adverse events are monitored when SGLT2 inhibitors are used in clinical practice.

Reference

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Abstracts in Focus

Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data

Objective: To characterize the determinants, time course, and risks of acute myocardial infarction associated with use of oral non-steroidal anti-inflammatory drugs (NSAIDs).

Design: Systematic review followed by a one-stage bayesian individual patient data meta-analysis.

Data sources: Studies from Canadian and European healthcare databases.

Review methods: Eligible studies were sourced from computerized drug prescription or medical databases, conducted in the general or an elderly population, documented acute myocardial infarction as specific outcome, studied selective cyclo-oxygenase-2 inhibitors (including rofecoxib) and traditional NSAIDs, compared the risk of acute myocardial infarction in NSAID users with non-users, allowed for time dependent analyses, and minimized effects of confounding and misclassification bias.

Exposure and outcomes: Drug exposure was modelled as an indicator variable incorporating the specific NSAID, its recency, duration of use, and dose. The outcome measures were the summary adjusted odds ratios of first acute myocardial infarction after study entry for each category of NSAID use at index date (date of acute myocardial infarction for cases, matched date for controls) versus non-use in the preceding year and the posterior probability of acute myocardial infarction.

Results: A cohort of 446 763 individuals including 61 460 with acute myocardial infarction was acquired. Taking any dose of NSAIDs for one week, one month, or more than a month was associated with an increased risk of myocardial infarction. With use for one to seven days the probability of increased myocardial infarction risk (posterior probability of odds ratio >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. The corresponding odds ratios (95% credible intervals) were 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and 1.58 (1.07 to 2.17) for rofecoxib. Greater risk of myocardial infarction was documented for higher dose of NSAIDs. With use for longer than one month, risks did not appear to exceed those associated with shorter durations.

Conclusions: All NSAIDs, including naproxen, were found to be associated with an increased risk of acute myocardial infarction. Risk of myocardial infarction with celecoxib was comparable to that of traditional NSAIDS and was lower than for rofecoxib. Risk was greatest during the first month of NSAID use and with higher doses.

Reference

Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, Brophy JM. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ. 2017 May 9;357:j1909. doi: 10.1136/bmj.j1909.

Diclofenac use and cardiovascular risks: series of nationwide cohort studies

Objective: To examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs, initiation of paracetamol, and no initiation.

Design: Series of 252 nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design).

Setting: Danish, nationwide, population based health registries (1996-2016).

Participants: Individuals eligible for inclusion were all adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases (that is, with low baseline risk). The study included 1 370 832 diclofenac initiators, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 healthcare seeking paracetamol initiators matched by propensity score, and 1 303 209 healthcare seeking non-initiators also matched by propensity score.

Main outcome measures: Cox proportional hazards regression was used to compute the intention to treat hazard ratio (as a measure of the incidence rate ratio) of major adverse cardiovascular events within 30 days of initiation.

Results: The adverse event rate among diclofenac initiators increased by 50% compared with non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7), 20%

compared with paracetamol or ibuprofen initiators (both 1.2, 1.1 to 1.3), and 30% compared with naproxen initiators (1.3, 1.1 to 1.5). The event rate for diclofenac initiators increased for each component of the combined endpoint (1.2 (1.1 to 1.4) for atrial fibrillation/flutter, 1.6 (1.3 to 2.0) for ischemic stroke, 1.7 (1.4 to 2.0) for heart failure, 1.9 (1.6 to 2.2) for myocardial infarction, and 1.7 (1.4 to 2.1) for cardiac death) as well as for low doses of diclofenac, compared with non-initiators. Although the relative risk of major adverse cardiovascular events was highest in individuals with low or moderate baseline risk (that is, diabetes mellitus), the absolute risk was highest in individuals with high baseline risk (that is, previous myocardial infarction or heart failure). Diclofenac initiation also increased the risk of upper gastrointestinal bleeding at 30 days, by approximately 4.5-fold compared with no initiation, 2.5-fold compared with initiation of ibuprofen or paracetamol, and to a similar extent as naproxen initiation.

Conclusions: Diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional non-steroidal anti-inflammatory drugs.

Reference

Schmidt M, Sørensen HT, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. BMJ. 2018 Sep 4;362:k3426. doi: 10.1136/bmj.k3426

Association between regular use of gastric acid suppressants and subsequent risk of Cholelithiasis: A prospective cohort study of 0.47 million participants

Background: Gastric acid suppressants have a major impact on gut microbiome which in turn, may increase the risk of cholelithiasis, but epidemiological evidence remains unclear. We undertook this research to evaluate the association between regular use of proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) with risk of cholelithiasis.

Methods: Prospective cohort study included 477,293 UK residents aged 37-73 years from the UK Biobank. We included the participants reported PPI or H2RA use, and were free of cholelithiasis or cancer. We evaluated hazard ratios (HRs) of regular use of PPIs or H2RAs and risk of cholelithiasis adjusting for demographic factors, lifestyle habits, the presence of comorbidities, use of other medications, and clinical indications.

Results: We identified 12,870 cases of cholelithiasis over a median follow-up of 8.1 years. Regular use of PPIs (HR 1.22 95% CI 1.16-1.29) or H2RAs (HR 1.16, 95% CI 1.05-1.28) was associated with an increased risk of cholelithiasis after confounding adjustment. There were no major differences among individual PPIs/H2RAs. The absolute risk of PPI-associated cholelithiasis was increased with the baseline predicted risk evaluated by known environmental and genetic risk factors (Risk differences in the lowest vs. the highest quartile: 1.37 vs. 4.29 per 1,000 person-years).

Conclusion: Regular use of PPIs and H2RAs was associated with increased risk of cholelithiasis. Future prospective studies are required to confirm whether the observed associations are casual.

Reference

Yang M, Xia B, Lu Y, He Q, Lin Y, Yue P, et al. Association Between Regular Use of Gastric Acid Suppressants and Subsequent Risk of Cholelithiasis: A Prospective Cohort Study of 0.47 Million Participants. Front Pharmacol. 2022 Jan 28;12:813587. doi: 10.3389/fphar.2021.813587

Hypersensitivity reactions to proton-pump inhibitors: Clinical presentation, diagnosis, and management

Background : Proton-pump inhibitors (PPI) are one of the most commonly prescribed drugs, and they are generally well tolerated. However, several immediate and delayed hypersensitivity reactions due to PPIs have been reported.

Objective: To review the clinical characteristics and management of immune-mediated immediate and delayed hypersensitivity reactions to PPIs.

Methods: We performed a search of a medical literature data base from January 1980 to October 2019 by using keywords that included "proton-pump inhibitors" and "hypersensitivity."

Results: Anaphylaxis is the most-common clinical presentation in patients with immediate hypersensitivity reactions to PPIs, followed by urticaria and/or angioedema. Occupational contact dermatitis, maculopapular eruption, fixed drug eruption, symmetrical drug-related intertriginous and flexural exanthema, and severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis have also been reported with PPIs.

Conclusion: The current knowledge and severity of the reported reactions indicated the importance of consideration of a causal relationship between hypersensitivity reactions and PPIs, and awareness of the existence of cross-reactivity among PPIs.

Reference

Kepil Özdemir S, Bavbek S. Hypersensitivity reactions to proton-pump inhibitors: Clinical presentation, diagnosis, and management. Allergy Asthma Proc. 2020 Mar 1;41(2):e37-e44. doi: 10.2500/aap.2020.41.190033

Waning of COVID-19 Vaccine Effectiveness and Safety Issues

High coverage of vaccination against COVID-19 was envisaged to end the pandemic when the vaccination was initially rolled out. However, rapid waning of vaccine-induced protection that has been fostered by data on vaccine-effectiveness against the currently circulating omicron SARS-CoV-2, a variant of concern (VOC). [1] In addition lack of transparency in clinical trial data, post-marketing data, and publications of vaccine associated adverse effects including those resulting in fatalities, is a growing concern.

A systematic review and meta-regression published in *The Lancet* provides robust evidence of waning vaccine-effectiveness over time. The authors identified 18 studies matching their inclusion criteria, of which three were randomised controlled trials (RCTs). Studies with participants of any age were included in the main analysis, with nine of 18 studies also including adolescents (aged ≥12 years). Information on sex or ethnicity distribution per study was not provided. Evidence from the meta-regression suggested a decrease in protection against SARS-CoV-2 infection by 21·0% (95% CI 13·9–29·8; on the basis of evidence from six studies) over a 6-month period from full vaccination across all ages and for all investigated vaccine types (Pfizer–BioNTech Comirnaty, Moderna-mRNA-1273, Janssen-Ad26.COV2.S, and AstraZeneca-Vaxzevria). Vaccine-effectiveness against severe disease decreased by 10·0% (95% CI 6·1–15·4; on the basis of evidence from five studies); however, vaccine effectiveness against severe disease remained higher than 70% for 6 months. Subgroup analysis of studies with older adults (as defined per study, but with a minimum age of 50 years) showed no statistically significant difference when compared with analyses of all ages. Variant-specific time analysis supported that reduced vaccine effectiveness does not only relate to alternating effectiveness against specific variants, but that waning immunity is probable.

The findings of Feikin and colleagues relate to the effect of waning immunity after full vaccination, without booster doses.[2] Furthermore, they are restricted to evidence before the emergence of omicron. A report on population-based surveillance data from the UK illustrated waning of protection against symptomatic disease after two-dose and three-dose vaccination schedules, which was also observed when infections by the omicron variant began. The decline of protection in the UK was more distinctive for omicron than for delta. With an mRNA-based booster dose (Pfizer-BNT162b2 or mRNA-1273), vaccine effectiveness against omicron reached more than 60% 2 weeks after the booster dose. Approximately 4 months after the booster, a decline in protection was noted. Similar to the findings of Feikin and colleagues, a reduction in vaccine effectiveness against severe disease (ie, hospitalisation) was observed after full vaccination; however, this reduction was less great than that observed after symptomatic infection. The protective effect against hospitalisation after omicron infection could be restored up to 90% with an mRNA vaccine booster; a decrease to 75% 3–4 months after the booster was noted.[4]

Preliminary data from Israel suggest an increased protective effect against infection (risk reduced by a factor of 2·0, 95% CI 2·0–2·1) and severe illness (risk reduced by a factor of 4·3, 2·4–7·6) 12 or more days after dose four when compared with people who received three doses.[3] Optimal vaccination strategies are being sought, and heterologous vaccination schedules, optimal time interval between doses, or variant-adapted vaccines are being discussed. The overall aim of vaccination against COVID-19 is to prevent severe disease and deaths. The prevention of severe disease is strongly related to the maintenance of a functioning health-care system, and thus combines the individual and public health risk of the COVID-19 pandemic. Therefore, the goal of public health measures is also to limit the spread of the virus and to interrupt transmission chains. Vaccination also has an effect on transmission rates; however the magnitude of effect changed in the light of arising VOCs.[1] A study from Denmark investigated household transmissions of the omicron and delta variant. The secondary attack rate was approximately 10% lower in households with fully vaccinated primary delta cases and 20% lower in households with booster-vaccinated primary delta cases, when compared with unvaccinated primary cases. Although a vaccine-induced reduction of transmission under omicron was also observed (but to a lesser extent), the findings underline that the continuing emergence of new VOCs poses a threat to reducing the spread of SARS-CoV-2. As most of the vaccines are based on spike protein, the antibodies against the spike protein may not offer significant protection when there are significant mutations involving the spike protein.

Besides the efficacy issues, reports on safety issues of different available vaccines against COVID-19 are coming up and serious adverse effects including myocarditis resulting in fatality and cerebral venous thrombosis have been reported.[5-7] Long-term safety studies to provide concrete evidence on favorable risk-benefit ratio, transparency in clinical trial/post-marketing data and exclusion of low-risk population from the coverage are prudent.[8-9]

Conclusion

In-depth evaluation of the level and duration of protection afforded by infection-induced immunity relative to vaccine-induced immunity and close monitoring of different types of adverse effects with comparison of all-cause morbidity and mortality in both the groups will be helpful in informed decision-making regarding the vaccination.

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Letrozole for Fertility Issues

Letrozole is a non-steroidal, highly selective oral aromatase inhibitor (AI), which can reversibly bind to the rate-limiting enzyme P450 aromatase in estrogen biosynthesis pathway and inhibit the conversion of testosterone to estradiol and androstenedione to estrone. The down-regulated estrogen increases the secretion of pituitary follicle-stimulating hormone (FSH) as feedback to stimulate ovulation.[1,2] Nowadays, letrozole has been extensively used for ovulation induction (OI) in anovulatory infertility and to augment follicles for ovulating women. Furthermore, letrozole is used as an adjunct for intrauterine insemination and in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles. Letrozole is also used for fertility preservation in women with estrogen-sensitive cancers. Studies have also shown the effectiveness of letrozole in endometrium preparation for frozen-thawed embryo transfer (FET).[1]

Pharmacology

Letrozole has proven to be a highly potent inhibitor of aromatase. Plasma kinetics of letrozole is characterized by a fast and complete absorption (t_{max}=1h) (the mean absolute bioavailability is 99.9%), and a rather slow elimination, the plasma half-lives of letrozole (2.5 mg once daily) are 41~48 hours after oral administration. The extent of letrozole absorption is not influenced by the intake of food. The major route of elimination is metabolism by CYP450 isoenzymes into an inactive carbinol metabolite. The $t_{1/2}$ of letrozole can markedly increase in hepatic impairment patients and caution is required.[1, 2]

Letrozole inhibits the aromatase activity by more than 99%, and endogenous estrogen synthesis by 97%-99%. The mechanisms of letrozole for OI remain unclear. However, it has been proposed that it may act through both centrally and peripherally mechanisms. Centrally, letrozole dramatically lowers the estrogen level, which prevents its negative feedback on the hypothalamic-pituitary-gonad (HPO) axis. Peripherally, as the conversion of androgen substrates to estrogen is inhibited, the temporary accumulation of intraovarian androgens may increase follicular sensitivity through amplification of FSH receptor gene expression. Also, androgens accumulation in the follicle may stimulate insulin-like growth factor 1 (IGF-1) and other endocrine and paracrine factors, which may synergize with FSH to promote folliculogenesis.[1]

Letrozole may be used alone or in conjunction with exogenous FSH for OI, but the optimal dose and regimen of letrozole is not yet clear. The protocol of letrozole for OI mimics the use of clomiphene citrate (CC). Typical treatment of letrozole consists of 2.5 to 7.5 mg daily taken during days 3~7 of menstrual for a 5-day course, which coincides with the availability of a 6~8mm follicle. The 6mm follicle is equipped with a high level of androgen receptors and increased androgen levels at this time promote granulosa cell mitosis and induction of FSH receptors.[1]

Ovulation induction followed by timed intercourse or intrauterine inseimination (IUI)

As letrozole does not inhibit negative feedback of estrogen to HPO axis, it usually induces single follicle development and avoids multiple pregnancies. It has a relatively short half-life (41~48 hours) estrogen target tissues (such as endometrium and cervical mucus) are potentially spared of adverse effects, as suggested by clinical and experimental data. Therefore, letrozole has less effect on endometrium thickness and receptivity, and it is more conducive to embryo implantation.[1]

The current recommendation is letrozole used as a first-line agent for PCOS and other WHO group II anovulatory patients. For ovulatory patients, letrozole is also commonly used to increase their chance of becoming pregnant. Typical diagnoses include mild male factor, endometriosis, pelvic factor, and advanced maternal age. Despite the advantage of letrozole in PCOS patients, letrozole and CC have similar outcomes in infertile women with mild oligoasthenospermia, early-stage endometriosis, and unexplained infertility who underwent time intercourse or intrauterine insemination (IUI).[1]

Letrozole for unexplained infertility

The diagnosis of unexplained infertility is despite intensive evaluation of both male and female partners, the etiology may remain unknown. It is identified in 10%–30% of couples seeking treatment for infertility. Letrozole would achieve mono-follicular development in most cycles, thereby may reduce multiple gestation pregnancy and OHSS, with a comparable pregnancy success rate with gonadotropins or CC, may become the first choice of treatment for unexplained infertility.[1]

Co-administration of letrozole during controlled ovarian stimulation

Mechanistically, letrozole administration in the early follicular phase during controlled ovarian stimulation (COS) significantly increased the levels of testosterone and androstenedione in

follicular fluid, which improved follicular sensitivity to FSH stimulation. For poor responders, some preliminary reports demonstrated a potential benefit of letrozole for improving ovarian response to FSH and reducing the number of gonadotropin doses but improved pregnancy outcomes. For normal/high responders, co-treatment with letrozole significantly lower gonadotropin consumption and reduce the incidence of OHSS, the pregnancy outcomes are similar or higher than the other groups. Adjunctive use of letrozole may also be an effective means of low-cost IVF therapy particularly in ICSI cycles.[1,3]

Letrozole in preparation of endometrium for FET

Letrozole is cheap, being patient-friendly, yielding at least equivalent pregnancy rates when compared with natural and artificial cycles with or without suppression and requires less luteal support than artificial cycles. For anovulatory patients, it may be a better choice than HRT (hormone-replacement therapy) for FET endometrium preparation in term of patient-acceptance and cost-efficacy analysis.[1]

Safety

Low-grade hot flashes, arthritis, arthralgia, and myalgia are more frequent in postmenopausal women with breast cancer after letrozole therapy.[1,2] Though the duration of OI using letrozole is much shorter than breast cancer treatment, study reported the sides effects are headache, hot flashes, abdominal bloating, and abdominal pain including cramps. Aromatase is particularly high expressed in temporal and frontal areas of the human brain, these regions are generally associated with learning, memory, sensory processing and dopaminergic activity. It is known that letrozole can cross the blood-brain barrier and inhibit the estrogen synthesis of hippocampal and results in cognitive dysfunction and other neurological symptoms. In clinical, treatment with AI has been reported to be associated with specifically impaired hippocampus-dependent memory, mood disturbances, somnolence, anxiety, fatigue, and hot flashes in some studies. Though letrozole is widely used for female infertility nowadays, attention from doctors and patients on the aforementioned adverse effects is warranted. Letrozole may well be safer in terms of teratogenicity because its half-life virtually assures elimination from the body before implantation. But before letrozole administration, pregnancy should always be ruled out.[1]

Conclusions

As a new type of OI drug, the application of letrozole is not only limited to the clinical treatment of OI for timed intercourse but also involves many aspects of infertility treatment. Besides, letrozole is more accessible and has fewer adverse side effects and lower cost than injectable gonadotropins.[1,4] Its superiority for OI in WHO group II anovulation patients has been confirmed by high-quality clinical and basic studies. The exact mechanism of OI by letrozole is not clear, the clinical applications are still in the experimental stage, and researchers have not yet reached a consensus on the standardized scheme. It is expected that large clinical samples of RCT and mechanism research will provide evidence and clear guidance for clinical application.[1]

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DARIDOREXANT

Daridorexant, formerly known as nemorexant, is a dual orexin receptor antagonist, which blocks the binding of the wake-promoting neuropeptides orexins and is thought to turn down overactive wakefulness, as opposed to treatments that generally sedate the brain.[1] Insomnia is characterized by difficulties with sleep onset and/or sleep maintenance and impairment of daytime functioning. It chronically affects the person's daily functioning and long-term health effects, as insomnia is often associated with comorbidities such as hypertension, diabetes, and depression.[1] Conventional treatments for insomnia include drugs targeting gamma-aminobutyric acid type-A (GABA-A), serotonin, histamine, or melatonin receptors; however, undesirable side effects are frequently reported, such as next-morning residual sleepiness, motor incoordination, falls, memory and cognitive impairment. Novel drugs that target orexin receptors gained increasing attention after discovering the role of orexin signalling pathway in wakefulness and almorexant, an orexin receptor antagonist that improved sleep. Daridorexant was designed via an intensive drug discovery program to improve the potency and maximize the duration of action while minimizing next-morning residual activity.[2]

Mechanism of action

Daridorexant works on orexin receptors OX1R and OX2R to block the binding of orexins, which are wake-promoting neuropeptides and endogenous ligands to these receptors. This mechanism avoids a more widespread inhibition of neuronal pathways and associated side effects that are intrinsic to positive allosteric GABA-A receptor modulators. It reduces overactive wakefulness: in the investigational trials, daridorexant reportedly improved sleep and daytime functioning in patients with insomnia.[2] It was approved by the FDA on January 10, 2022, under the name Daridorexant.3 as the second orexin receptor antagonist approved to treat insomnia following suvorexant.

Phrarmacokinetics

Daridorexant reaches peak plasma concentrations within one to two hours. Daridorexant has an absolute bioavailability of 62%. While a high-fat and high-calorie meal delayed the Tmax by 1.3 hours and decreased the Cmax by 16% in healthy subjects, the total exposure (AUC) was not affected.[4] Daridorexant has a volume of distribution of 31 L. The blood to plasma ratio is 0.64.[4] It effectively passes the blood-brain barrier. It is 99.7% bound to plasma proteins. It undergoes extensive metabolism primarily mediated by CYP3A4 (89%), mostly via oxidative transformations.[3] Other CYP enzymes individually contribute to less than 3% of metabolic clearance of daridorexant.[4] The terminal half-life is approximately 8 hours.[3]

Adult dosing for insomnia

25 mg to 50 mg once per night to be taken orally within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening. [5] Time to sleep onset may be delayed if taken with or soon after a meal. No dose adjustment is recommended in case of renal impairment, but in case of moderate hepatic impairment (Child-Pugh score 7-9) 25 mg per night is the maximum dose and it is not recommended in severe hepatic impairment (Child-Pugh score ≥10). With strong CYP3A4 inhibitors concomitant use is to be avoided and with moderate CYP3A4 inhibitors, the maximum recommended dose is 25 mg per night. With moderate or strong CYP3A4 inducers concomitant use is to be avoided.

Indication

Treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Adverse effects: [5]

Important adverse effects involve central nervous system and include worsening depression and suicidal thoughts, hallucinations, headache, sleep paralysis for up to several minutes, complex sleep behaviors such as sleep-walking, sleep-driving, preparing and eating food, making phone calls, having sex or doing other activities while not fully awake that may not be remembered the next morning. Fatigue, dizziness and nausea have also been reported.

Conclusion

Dual orexin receptor antagonists (DORAs) represent a novel type of sleep medication that provides an alternative to the traditionally used positive allosteric gamma-aminobutyric acid (GABA)-A receptor modulators. Daridorexant is indicated specifically for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance in adults.

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Stockley's Drug Interactions: Resource for Drug Information

Stockley's Drug Interactions (12th Revised edition, Pharmaceutical Press; Mar. 2019) edited by Claire L Preston**,** is an updated **s**ource book of interactions, their mechanisms, clinical importance and management. It remains the world's most comprehensive and authoritative international reference book on drug-interactions. It provides expertly authored advice on managing drug interactions, and will quickly and reliably help health-care provides decide the best course of action.

Based upon thousands of published papers and reports it:

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- Provides comprehensive details of the clinical evidence for the interactions under discussion, an assessment of their clinical importance, and clear guidance on managing the interaction in practice
- Each monograph has a brief summary of the interaction – perfect for the busy healthcare professional
- Based on published sources and fully referenced throughout
- Contains almost 500 new monographs,
- Global coverage - inclusion of drugs used worldwide

Stockley's summarizes a broad range of references. Product information is often inherently cautious and incomplete, so this edition reviews these sources (from the UK and USA) alongside extensive primary literature (case reports and clinical papers) and guidance from international regulatory bodies such as the UK Medicines and Healthcare products Regulatory Agency.

Drug–drug, drug–food and a limited number of drug–herb combinations are indexed for both interacting and some non-interacting pairs. The fully referenced monographs (approximately 4500 of them) are clearly laid out with a brief summary of the interaction, clinical evidence, proposed mechanism and importance, and practical management advice. Monographs also include alternative non-interacting drug options as far as applicable.

With the extensive coverage and ease of use, this important resource book should appeal to all prescribers looking for detailed information on drug-interactions.

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KEY MESSAGES OF THE ISSUE

1. The first line treatment for *P.vivax, P.ovale,P.malariae or P.knowlesi* is chloroquine given for for 3 days. The recommended second-line option in Nepal is dihydroartemisinin + piperaquine (DHA/PPQ). The longer half-life of piperaquine gives it an advantage over lumefantrine in the treatment of vivax malaria. It is programmatically most suitable to have the same medicines as second line for both vivax and facilparum malaria. So, DHA/PPQ is also the second- line ACT for P. falciparum in Nepal. Second line antimalarial (DHA/PPQ) should be used when a patient does not tolerate or has adverse reactions to the first line medicine and in case of reappearance of symptoms and parasites within 28 days following initial antimalarial treatment of the first-line drug. The first line treatment for falciparum malaria is artemether + lumefantrine (AL) given over three days and a single dose primaquine.
2. SGLT2 inhibitors significantly reduce the risk of acute kidney injury, and show the reduced trend in the risk of severe hypoglycemia; whereas this drug class significantly increase the risks of diabetic ketoacidosis, genital infection, and volume depletion, and show the increased trends in the risks of fracture, amputation, and urinary tract infection, regardless of type of underlying diseases and type of SGLT2 inhibitors

3. All NSAIDs have been associated with an increased risk of acute myocardial infarction. Risk of myocardial infarction with celecoxib was comparable to that of traditional NSAIDS and was lower than for rofecoxib. Risk is greatest during the first month of NSAID use and with higher doses.
4. Diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional non-steroidal anti-inflammatory drugs. Diclofenac initiation also increased the risk of upper gastrointestinal bleeding at 30 days, by approximately 4.5-fold compared with no initiation, 2.5-fold compared with initiation of ibuprofen or paracetamol, and to a similar extent as naproxen initiation.
5. Regular use of proton pump inhibitors (PPIs) and H2 receptor blockers has been found to be associated with increased risk of cholelithiasis. Anaphylaxis is the most-common clinical presentation in patients with immediate hypersensitivity reactions to PPIs, followed by urticaria and/or angioedema.
6. Waning vaccine-effectiveness for COVID-19 vaccine within a short period of time and safety issues are coming up and serious adverse effects including myocarditis resulting in fatality and cerebral venous thrombosis have been reported. There should also be ongoing evaluation of the protection afforded by infection-induced immunity relative to vaccine-induced immunity with comparative assessment of all-cause morbidity and mortality in vaccinated and unvaccinated population for evidence-based decision making.
7. Letrozole has been extensively used to induce ovulation in anovulatory infertility and to augment follicles for ovulating women. Furthermore, letrozole is used as an adjunct for intrauterine insemination and in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) cycles. Letrozole is also used for fertility preservation in women with estrogen-sensitive cancers. Adverse effects associated with it are impaired hippocampus-dependent memory, mood disturbances, somnolence, anxiety, fatigue, and hot flashes.
8. Daridorexant, a dual orexin receptor antagonist representing a novel type hypnotic agent, is an alternative to the benzodiazepines and non-benzodiazepines. It is indicated specifically for the treatment of insomnia characterized by difficulties with sleep onset and/ or maintenance in adults. Important adverse effects include worsening depression and suicidal thoughts, hallucinations, headache, sleep paralysis for up to several minutes, complex sleep behaviors such as sleep-walking, sleep-driving etc.

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