Peradeniya Medical School Alumni Association -PeMSAA Australasia

PeMSAA Newsletter

July 2018
Volume 1, Issue 4

Message from Treasurer PeMSAA Australasia

Welcome to the Fourth publication of the PeMSAA Australasia newsletter.

We are just three months away from long awaited 10th Anniversary PeMSAA Australasia congress to be held in world famous Adelaide Oval in South Australia from 12th to 14th October 2018.

After the privilege of organizing this event was given to South Australia, our team has been tirelessly working to uplift PeMSAA Australasia's activities, most importantly refurbishing our website; where all the activities of PeMSAA Australasia are now easily accessible. As the treasurer, it has been a pleasure to oversee the growth of PeMSAA Australasia's financial maturity. Our financial situation is still in it's infancy, however, with increasing interest in PeMSAA Australasia it is a pleasure to see that new life members have joined our organization. Our Membership number has grown from 46 when we took over the office to a considerable total. I would like to take this opportunity to welcome the new members and their families to PeMSAA Australasia. At the same time I like to express my sincere gratitude to our hard working state PeMSAA representatives for their effort.

Finally, I would like to take this opportunity to invite you to join PeMSAA Australasia as a member and more importantly join us at the 6th PeMSAA Australia Congress in October respecting our alma mater.

Dr Janakie Ratnayake, Treasurer - PeMSAA Australasia

Inside this issue

Registration Now open 6th PeMSAA Australasia Congress - Adelaide Oval

12– 14th October 2018

- Two Adelaide sightseen Pre Congress tours 12.10.18
- Reception 12.10.18
- Academic sessions 13 & 14th October
- Gala dinner 13.10.18
- Thaala 2018 with BnS 14.10.18
- PeMSAA Australasia Post Congress Trip From Adelaide to Melbourne via Great Ocean Road

REFINING METFORMIN PRESCRIBING IN NEW ZEALAND

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Abstract

Metformin is the mainstay of treatment of type 2 diabetes. However, there has been significant concern on prescribing metformin in patients with renal impairment as a result of metformin related lactic acidosis (MALA). Recent studies have cast doubt on the existence of MALA purely related to metformin use. Medsafe recently initiated changes to datasheet so lower doses of metformin could be used in patients with GFR down to 15ml/min. In this paper we outline the context and implications of this change.

Introduction

For many years metformin has been the mainstay of pharmacological treatment of patients with Type 2 diabetes. The International Diabetes Federation, the American Diabetes Association and European Association for the Study of Diabetes recommend that metformin be commenced as the first-line treatment in all newly diagnosed patients, regardless of age.

The discovery of metformin can be traced back to the pioneering work with extracts of the herb Galega officinalis in early 20th century, which led to the characterisation of the blood lowering effects of an active ingredient named galegine. Metformin has a significant effect on blood glucose levels and reduces mortality compared to other therapeutic modalities and the risk of cardiovascular disease.

Based on medium sized cohort study with 10 year follow up metformin may be associated with a reduction in cancer risk . It helps in weight reduction and seems to prolong survival in experimental models and will be tested for anti-aging effect in humans .

In general metformin is well tolerated, although may cause nausea, vomiting or diarrhoea in some patients especially if introduced at a high dose or taken on an empty stomach. Vitamin B12 deficiency is a less common side effect and occasional measurement of Vitamin B12 levels in patients on long term metformin therapy is prudent Lactic acidosis is a spectre that has hung over metformin ever since its introduction because other biguanides, phenformin and buformin (long since withdrawn from the market) - were clearly associated with an increased rate of lactic acidosis. This association has resulted in application of restrictions on use of metformin, not taking into account the different pharmacokinetics. The question arises as to whether metformin can induce lactic acidosis on its own and, in the normal course of events the answer is probably no or, if it does, it is exceedingly rare. However, metformin is known to raise lactate levels in humans but magnitude of this increase is small. Overdose of metformin can result in raised lactic acid levels and in serious overdose lactic acidosis may occur even in healthy individuals .In animals and humans, metformin administration is associated with an increase in blood lactate levels. The increase in plasma lactate concentration with therapeutic doses of metformin is small, usually < 2 mmol/L, although higher levels may occur . In patients with lactic acidosis lactate levels usually raised above 5mmol/L.Lactic acidosis is most commonly associated with tissue ischaemia such as in septic shock, burns, limb ischaemia, seizures, trauma, severe dehydration, cardiac arrest or cardiogenic shock and may be aggravated by hepatic and renal dysfunction, alcohol, respiratory insufficiency and elevated levels of metformin. It is likely that in most cases of lactic acidosis occurring in patients taking metformin, other causes have been major contributors. Metformin associated lactic acidosis (MALA) has a high mortality but the rates have decreased from 50% to 25% in recent studies .

A Cochrane review failed to identify any cases of lactic acidosis in patients taking metformin. However, a Dutch observational study found an incidence of 47 cases of metformin associated lactic acidosis per 100,000 patient years but the outcome of MALA was determined by the severity of the underlying disease rather than by metformin itself however, in other studies the highest estimates are ≤10 events per 100,000 patient-years of exposure . Even though large case series have given polar opposite results, cases of lactic acidosis associated with metformin use have been reported regularly. There may be a link between metformin use and lactic acidosis though a systematic review suggested that other factors may be implicated .

Renal impairment is a particular risk in patients with Type 2 diabetes, in part because of the incidence of diabetic nephropathy, but also they are usually in an older age group and they may also have co-morbidities such as hypertension that may play an aetiological role in renal damage. Metformin is not metabolised in the body but transported through the body by transporters and is actively excreted unchanged by the kidneys. Reduction in glomerular filtration rate reduces active excretion of metformin and can be associated with an increase in plasma concentration of the drug. It is considered that a plasma metformin level of <5mg/L is safe and does not carry any significant risk of lactic acidosis. Previous advice has been that metformin was contraindicated in patients with a creatinine clearance <60ml/min. However, some health authorities have reset the contraindication at 30ml/min . Recently an Australian group has studied pharmacokinetics of metformin, both normal and sustained release preparation in healthy subjects and patients. The group assessed dose-response curves of metformin in healthy subjects and patients with Type 2 diabetes, and then by modelling have developed maximum metformin doses in relation to creatinine clearance that will maintain plasma metformin levels <5mg/L Medsafe has evaluated this data and have now made changes to the New Zealand data sheet for metformin incorporating the information from this paper. These recommendations are shown in table 1

Table 1 Recommendation of Metformin dose based on creatinine clearance

Creatinine clearance	Maximum daily dose of metformin
15-30 mL/min	500mg
30-60 mL/min	1000mg
60-120 mL/min	2000mg

In practice GFR is often estimated using alternative methods to Cockroft Gault, such as the MDRD or CKD-EPI equations, and also adjusted to a surface area of 1.73 m^2. All these equations produce an acceptable estimation of GFR, although in patients with lower GFR, the MDRD and CKD-EPI equations have higher accuracy compared to the Cockroft-Gault . The CKD-EPI equation was developed using measured GFR that was adjusted for surface area . When using GFR expressed as mL/min/1.73m^2 to adjust dose, patients who have a low surface area may as a result be overdosed and patients with a high surface area may be under dosed . Hence, at extremes of body size it would be advisable to base the dose adjustment on total GFR, expressed in mL/min, instead of GFR adjusted for surface area, expressed as mL/min/1.73 m^2. The conversion can be performed by multiplying the estimate of GFR expressed as mL/min/1.73m^2 by the patients surface area divided by 1.73m^2.

What does this mean for our patients and prescribers? Firstly it is reassuring to have these scientifically based guidelines for metformin dosing in patients with Type 2 diabetes with stable renal impairment, which permit metformin therapy to continue down to a creatinine clearance of 15ml/min, with appropriate dose adjustment. Secondly patients may not need to change to other medication which could be less desirable. Thirdly in the past it is likely that higher dosage of metformin was continued in many patients with moderate renal failure without appropriate guidance or dose adjustment and perhaps contributed to some cases of lactic acidosis, so using lower doses may lead to safer use of metformin.

However there are some unresolved issues. These recommendations are not based on randomised controlled trial data. Efficacy of metformin at lower doses in patients with renal failure has been questioned by some and needs to be studied further. It is well known that lower doses of metformin works in early type 2 diabetes and so it is likely to be effective in patients with renal impairment. There may be a case for metformin measurements when used in patients with very low GFR but the assay is not routinely available in New Zealand. Measurement of venous lactate levels may be a potential alternative in high risk situations.

Metformin should not be used when the GFR is <15mls/min. Adam et al predicted plasma metformin level of 4.4mg/litre at GFR of 10ml/min when 500mg /day metformin dose was used. Although the risk of MALA does not seem to be increased and the progression to end-stage renal disease is significantly lower, patients on metformin at this level of renal function have significantly higher all-cause mortality .

Like many other medicines, prescribers need to be vigilant for side effects and adjust the dose of metformin accordingly but unfortunately this is often forgotten. Renal function should be checked regularly in patients on metformin. We suggest renal function testing annually for patients with creatinine clearance >80ml/min, six monthly for patients 30-80ml/min and three monthly for patients <30ml/min or more frequently in patients at particular risk of renal function deterioration e.g. commencement of ACE inhibitors or NSAIDs. Metformin doses should be adjusted according to the results.

Medsafe is to be congratulated for their initiation of these changes for metformin in the context of renal impairment. This is fairly unique, where the regulatory agency takes an active step in improving dosing recommendations. Suggested changes should allow continuation of this valuable medication at a lower dose in patients with Type 2 diabetes, despite declining renal function. Several authors have advocated the liberalisation of metformin therapy in the context of renal impairment (23, 24) Patients should be warned to discontinue metformin during serious acute illness especially leading to dehydration and serious infections to minimise any aggravation of the risks for lactic acidosis. Insulin can always be used as a short term substitute for glycaemic control. Prescribers should be vigilant in monitoring side effects and reporting them to CARM especially when used in patients with moderate to severe renal impairment. These reports can be made electronically through the CARM website.

Dr Sisira Jayathissa

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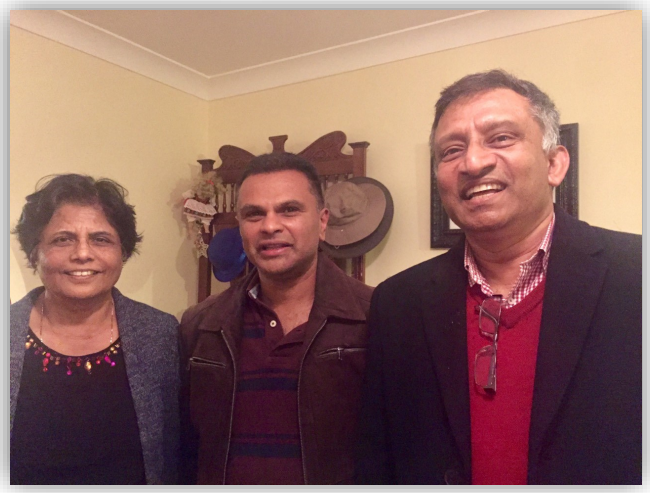
PeMSAA's Next Destination! - Sydney 2019—2021
Harbour Bridge and the Opera House at dusk...

New South Wales Membership Drive

On the 2nd of June 2018, the New South Wales Membership Drive was held in Sydney formidably. This was very well attended, even by a former president of PeMSAA Australasia, Dr Malini Arumugam. The initiation of this Membership Drive was led by one of our NSW representatives Dr Anura Thalagala, of Sydney. It was pleasing to note that this Membership Drive served its purpose well, and attracted quite the group of active new members!







A few photographs of this Membership Drive are below:

Once again a very big thank you to the NSW representatives for their great work!

NSW Representatives:

Dr Anura Thalagala Dr Saubagya Gunathilaka Dr Chandrika Yapa

Dr Ravi Senadeera Dr Padma Kaluarachchi

Our New Website— http://www.pemsaaaustralasia.org/

6th PeMSAA Australasia Congress Registration is now open

Welcome New PeMSAA Australasia Life Members!

16.	Dr Dayani Jayakody	South Australia
17.	Dr Priyan Yapa	South Australia
18.	Dr Shanthi Bandara	South Australia
19.	Dr Saubhagya Gunathilaka	NSW
20.	Dr Ravinda Chandrasekara	NSW

PeMSAA Australasia Committee Members 2017-2018

President	Dr Nayanananda Lekamge
Secretory	Dr Shantha Sooriyabandara
Treasurer	Dr Janakie Ratnayake
New Zealand	Dr Sisira Jayathissa (Immediate past president)
	Dr Lakashman Bandara

State Representatives

South Australia (2018 Congress Organising Committee)	
	Dr Priyan Yapa
	Dr Shathi Bandara
	Dr Priyanka Perera
	Dr Kumara Ekanayaka
	Dr Ravi Ruberu
New South Wales	Dr Malini Arumugam
	Dr Anura Thalagala
	Dr Nimmi Athuraliya (Editor)
Queensland	Dr Sri Varman
	Dr Lakal Dissabandara
	Dr Akila Samarakkody
Victoria	Dr Tissa Wijerathne
	Dr Shalini Wickramasinghe
	Dr Janaka Thennakoon
	Dr Shiran Wijerathne
Western Australia	Dr Senarath Werapitiya
	Dr Chandrasiri Premarathne
Australia Capital Territory	Dr Kalyana Rodrigo
	Dr Dharshani Gunaratne
Tasmania	Dr Kapila Idirimanna
	Dr Kshendra Thilakaratne

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