6 November 2019

Ms Michelle Sweidan
Editor, Therapeutic Guidelines Limited
Ground Floor, 473 Victoria St
West Melbourne, VIC 3003
msweidan@tg.org.au

Dear Ms Sweidan

RE: Review of Therapeutic Guidelines: Gastrointestinal

The Society of Hospital Pharmacists of Australia (SHPA) is the national, professional, for-purpose organisation for leading pharmacists and pharmacy technicians working across Australia's health system, advocating for their pivotal role improving the safety and quality of medicines use.

SHPA welcomes the opportunity to provide comments regarding Therapeutic Guidelines: Gastrointestinal, ahead of its revision for the next edition. This guideline is an essential reference for our members who work in gastroenterology and hepatology units, any inpatient, outpatient, ambulatory or primary care settings where patients of any age with gastrointestinal conditions, receive pharmacy services. SHPA convenes a Medical Specialties Practice stream, and its members have raised issues and considerations in the current version of Therapeutic Guidelines: Gastrointestinal for the Editorial Board to review ahead of the next version.

Hepatitis C

SHPA recommends a thorough update of the hepatitis C section as the guidelines are out of date. This is expected considering the recent approval and listing of curative hepatitis C medicines. The *Australian recommendations for the management of hepatitis C virus infection: a consensus statement*[1] should be used as a reference for updating the section as the consensus statement is updated more regularly in comparison to the Therapeutic Guidelines. This will factor in the expected developments in hepatitis C over the coming years.

Examples of direct acting antivirals for hepatitis C

The table should be expanded to include NS5A inhibitors velpatasvir, pibrentasvir, voxilaprevir and NS3/4A protease inhibitor, glevaprevir.

Additionally, consideration should be made to remove simeprevir, paritaprevir, dasabuvir and ombitasvir as these are no longer considered as optimal antivirals for the treatment of hepatitis C, and are not listed on the Pharmaceutical Benefits Scheme.

Examples of antiviral regimens for adults with hepatitis C

SHPA suggests that there should be an inclusion for a regimen for those patients who may fail to respond to the initial treatment or may have a resistant strain of virus. In this instance, practitioners should be advised to use sofosbuvir/velpatasvir/voxilaprevir combination for 12 weeks or glecaprevir/pibrentasvir for 16 weeks.

Hepatorenal syndrome

Terlipressin

Recent research has highlighted that terlipressin given by continuous intravenous infusion results in lower adverse events compared to administration by intravenous boluses[2]. Consequently, SHPA believes that the Therapeutic Guidelines should note this change as practice in hospitals reflects this shift in administration, especially when treating patients who are awaiting a transplant. An example starting dose is 1.7–2.55 mg (terlipressin base) over 24 hours with gradual up-titration to maximum 10.2 mg per 24 hours. Gradually wean infusion down again once recovered, for example, reduce by one vial (0.85mg) every 24 hours. For terlipressin bolus dosing, more frequent doses should be permitted such as 1-2 mg up to 4-hourly. This allows for pharmacokinetics as the effect of the medicine usually wears off after 3-4 hours.

Bleeding oesophageal varices

Carvedilol

SHPA recommends the addition of carvedilol as an alternative to propranolol for prevention of variceal bleeding. A review has highlighted that there is no benefit or harm found for carvedilol compared with propranolol[3]. SHPA members have reported that in practice carvedilol is used often in preference as there is a theoretical additional reduction in portal hypertension due to the alpha$_1$ blocking effects of carvedilol. The recommended dose should initially be 3.125-6.25mg daily up to 12.5mg daily as tolerated (hypotension). Additional caution should be included with carvedilol use, that hypotension is more likely compared with propranolol. If hypotension is an issue, a dose split into twice daily should occur.

Terlipressin

The Therapeutic Guidelines should consider making terlipressin as the medicine of choice for acute bleeding, with octreotide as second-line where terlipressin is not available. There is evidence that terlipressin improves mortality[4], however, there is no evidence for octreotide doing as such. The frequency of dosing for terlipressin should be changed as a result, to 4 to 6-hourly, as this is the dose range used in a majority of studies[4].

Portal vein thrombosis

SHPA members would appreciate guidance on the appropriate use of medicines for portal view thrombosis. Specifically, SHPA members would invite discussion on the medicines currently used and the appropriate duration of treatments and doses, such as enoxaparin, warfarin and direct acting oral anticoagulants.

With respect to the use of warfarin in portal vein thrombosis, there are difficulties in INR to monitor treatment in patients with significant coagulopathy due to cirrhosis. Similarly, there is a risk of unreliability of factor Xa level monitoring for enoxaparin when bilirubin is significantly elevated. In these cases, referral to haematology is warranted.

Hepatocellular carcinoma

For patients with advanced hepatocellular carcinoma and compensated cirrhosis (CTP class A), sorafenib, a multikinase inhibitor, has been shown to prolong survival[5] and is regarded as the standard of care. Recommended use should be sorafenib 400 mg orally, twice daily. Sorafenib may have significant adverse effects, requiring pre-emptive or adjunctive treatment such as the management of hypertension, podiatry review, moisturisers, dose reduction or cessation. Sorafenib should not be used in patients with decompensated cirrhosis. Patients with decompensated cirrhosis and advanced HCC should receive supportive care only.

The new update of the guidelines should include Lenvatinib for the treatment of hepatocellular carcinoma as well with the recommended dosage of 12mg daily, orally.

Cystic fibrosis and biliary cirrhosis

SHPA recommends the addition of dosing for ursodeoxycholic acid of 20 mg/kg/day, divided doses as per Cochrane review[6]. The Therapeutic Guidelines should mention the benefits of the medicine and when to start the treatment.

There is no mention of vitamin K and other medicines that may need to be dose adjusted or ceased in the context of cystic fibrosis liver disease. Additionally the guidelines should include information on cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy on cystic fibrosis liver disease and associated adverse effects of CFTR modulators as some can cause elevations in liver enzymes.

Alcoholic liver disease

Although SHPA acknowledges that the evidence for acetylcysteine to treat alcoholic liver disease is poor at present, SHPA would still appreciate discussion of and consideration to inclusion of a dosage guide in the next edition. In hospitals, the dosage and administration of acetylcysteine for patients with alcoholic liver disease is a frequently asked question by medical officers.

Pruritis in cholestatic liver disease and cholestasis of pregnancy

A note should be added for ursodeoxycholic acid as included in the section on primary sclerosing cholangitis to maintain consistency across the guidelines. The note should be similar to the following:

"At the time of writing, ursodeoxycholic acid is not listed on the Pharmaceutical Benefits Scheme (PBS) for this indication. See the PBS website for current information."

Additionally, the Therapeutic Guidelines should mention the role and efficacy of antihistamines, such as cetirizine, that are prescribed for itchiness related to liver diseases.

If you have any queries or would like to discuss our submission further, please do not hesitate to contact Johanna de Wever, General Manager, Advocacy and Leadership on jdewever@shpa.org.au.

Yours sincerely

Kristin Michaels
Chief Executive

References

[1] Hepatitis C Virus Infection Consensus Statement Working Group. (2018). Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia .

[2] Cavallin, M., Piano, S., Romano, A., Fasolato, S., Frigo, A. C., Benetti, G., Gola, E., Morando, F., Stanco, M., Rosi, S., Sticca, A., Cillo, U. & Angeli, P. (2016). Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology, 63: 983-992. doi:10.1002/hep.28396

[3] Zacharias, A. P., Jeyaraj, R., Hobolth, L., Bendtsen, F., Gluud, L. L. & Morgan, M.Y. (2018). Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. Cochrane Database of Systematic Reviews. Issue 10. Art. No.: CD011510. DOI: 10.1002/14651858.CD011510.pub2.

[4] Ioannou, G.N., Doust, J. & Rockey, D.C. (2003). Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD002147. DOI: 10.1002/14651858.CD002147.

[5] Gomaa, A., & Waked, I. (2017). Management of advanced hepatocellular carcinoma: review of current and potential therapies. *Hepatoma Research*, *3*(6), 112. doi: 10.20517/2394-5079.2017.03

[6] Cheng, K., Ashby, D.& Smyth, R.L. (2017). Ursodeoxycholic acid for cystic fibrosis-related liver disease. Cochrane Database of Systematic Reviews. Issue 9. Art. No.: CD000222. DOI: 10.1002/14651858.CD000222.pub4