Terlipressin - current and emerging indications in chronic liver disease

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Abstract

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Terlipressin is an analogue of vasopressin that has potent vasoactive properties and has been available for use in most countries for nearly two decades. It has both established roles and emerging indications in the management of complications of decompensated chronic liver disease. We explore historic and emerging literature regarding the use of terlipressin for a range of indications including hepatorenal syndrome, portal hypertensive bleeding and disruptions in sodium homeostasis. Novel methods of infusion based terlipressin administration including the beneficial effect in reduction of adverse events are explored, in addition to new indications for the use of terlipressin in decompensated cirrhosis in an outpatient setting.

Keywords:

Terlipressin, Hepatorenal syndrome, cirrhosis, portal hypertension

Terlipressin is an analogue of vasopressin that has potent vasoactive properties and has been available for use in most countries worldwide for nearly two decades. Terlipressin acts through the V1a receptors which are located predominately on vascular smooth muscle within the splanchnic circulation, resulting in splanchnic vasoconstriction (1). The terlipressin induced splanchnic vasoconstriction gives rise to increased renal blood flow and has beneficial effects on hepatorenal syndrome (HRS) whilst at the same time reducing portal pressure and playing a role in reducing the risk of portal hypertensive bleeding.

These unique effects of the drug have translated into terlipressin playing a crucial role in the management of HRS and variceal bleeding for many years. Over more recent times there has been an expansion of the indications for terlipressin usage and a broadening in the methods available for drug delivery. Its established roles and emerging indications will be examined in this review.

Terlipressin for HRS

For clinicians who regularly use terlipressin there is little doubt in their minds regarding the efficacy of this drug for the treatment of HRS. However, issues with trial design in this area and strict registration criteria with the Food and Drug Administration (FDA) mean that terlipressin is still not available for use within the United States. Table 1 shows the key studies examining the use of terlipressin for the management of HRS.

(Table 1 to be inserted here)

The original studies describing the efficacy of terlipressin in the treatment of HRS now date back more than 20 years (2), with multiple publications subsequently demonstrating terlipressin to be effective in improving renal function in patients with HRS (3-14). One of the first case series published in 2000 described a small case series involving 9 patients (4). All had HRS as defined by the diagnostic criteria stipulated by The International Club of Ascites (ICA) (15) including; 1) low glomerular filtration rate (GFR), as indicated by serum creatinine (SCr) greater then 133 µmol/L; 2) absence of shock, ongoing bacterial infection, fluid losses and treatment with nephrotoxic drugs; 3) no improvement of renal function following diuretic withdrawal and plasma volume expansion; proteinuria less than 500mg/day and 5) no renal tract obstruction on imaging. Terlipressin was administered at a dose of 0.5-1mg 4 hourly for 15 days or until SCr fell to <133µmol/L. A reversal of HRS was defined as a reduction in SCr to <133 µmol/L and was achieved in 7 of the 9 patients. With the substantial limitation of the lack of a control arm, significant improvements from baseline included reduction in SCr and increase in serum sodium, 24hr urinary volume and mean arterial pressure (MAP) ($p<0.05$). Despite these promising results, the beneficial effects of terlipressin for HRS needed to be proven in larger randomised control trials (RCT).

The first prospective RCT of terlipressin for HRS was published by the New Delhi Group in 2003 (3). This study's inclusion criteria stipulated a SCr of >221µmol/L or 50% reduction in creatinine clearance within a 2 week period in addition to the ICA criteria for HRS. Group A (n=12) were randomised to 1mg terlipressin BD and Group B (n=12) received placebo. Both groups also received renal dose dopamine for the first 24-48 hours following enrolment. The terlipressin group achieved a significant decrease in SCr compared to placebo at day 8. No comparative data is available for day 15 SCr as no patients in the placebo arm survived to this time point. There was a survival benefit at D15 in those treated with terlipressin ($p<0.05$), however

participants were not followed beyond day 15 limiting conclusions regarding long-term survival or sustained HRS reversal.

A second larger RCT was thereafter conducted in Italy, including secondary outcomes to determine the benefit of terlipressin on intermediate and long-term survival (8). Group A (n=26) received 1mg Terlipressin TDS for 5 days and then subsequently 0.5mg TDS for an additional 14 days in conjunction with intravenous (IV) albumin. Group B (n=26) received IV albumin infusions alone. Both groups were followed for 3 months and if initial response was achieved, retreatment with the same regimen was allowed if HRS recurred. Survival was greater at day 15 and 180 in those treated with terlipressin ($p<0.05$) and patients in Group A were more likely to achieve reversal of HRS (SCr <133µmol/L) compared with group B ($p<0.05$).

With the promising results of these two small RCTs, a larger multicentre RCT was performed in the USA in 2008 (6). This study established a more stringent primary endpoint compared to other HRS RCTs being, '*treatment success*', defined as those participants at day 14 with resolution of HRS, with a documented SCr <133µmol/l, on two occasions, at least 48hrs apart without intervening transplantation, dialysis or death. In this third RCT 112 patients with decompensated cirrhosis were randomised across 35 centres to either terlipressin or placebo. The terlipressin group were initially treated with 1mg QID which was increased at day 3 to 2mg QID if the SCr had not fallen by at least 30% from baseline. '*Treatment success*' was achieved by 14/56 (25%) patients in the terlipressin arm and 7/56 (12.5%) patients in the control arm, however this difference did not reach statistical significance ($p=0.093$). Regarding the endpoint commonly used in the earlier RCTs of reduction of SCr to <133µmol/L on one occasion, the terlipressin group did achieve a superior result compared with the control arm ($p<0.05$). There was no survival benefit at any time point to day 180 ($P>0.05$).

In an attempt to get terlipressin approved for HRS in North America a second large RCT was subsequently performed (16). The terlipressin cohort (n=97) received 1mg QID which was increased to 2mg QID at day 4 if SCr hadn't decreased by >30% from baseline. The control group (n=99) received albumin infusion alone. The primary end-point was '*confirmed HRS reversal*' defined as SCr <133µmol/L on 2 occasions, at least 40 hours apart, within 24 hours of the last dose of terlipressin. More patients treated with terlipressin compared to placebo achieved '*confirmed HRS reversal*' (19.6% vs 13.1%) however this did not reach statistical significance (p=0.22). There was, however, a significant reduction in mean SCr from baseline to end-of-treatment in the terlipressin group compared to placebo (p<0.001).

Although this study failed to achieve the primary endpoint, potential issues within the study were identified. Of note, 3 patients within the terlipressin group who achieved reversal of HRS (creatinine <133 µmol on one occasion) were discharged from hospital before a second creatinine could be collected and thus were not included as achieving *confirmed HRS reversal*. The failure of this most recent large RCT to show a clear benefit of terlipressin for the management of HRS Type 1 has resulted in the lack of availability of this medication in the USA. Further studies of the use of terlipressin for HRS are currently underway in North America to hopefully provide the data necessary for FDA registration.

The large variation in response rates to terlipressin therapy may be related to the difference in mean SCr at baseline in these studies. The greater response rates in regards to reversal of HRS in patients treated with terlipressin in combination to albumin, relative to those in who received albumin therapy along, was seen in studies with a lower mean baseline SCr of 256µmol/L, 248µmol/L and 255µmol compared with an alternate study in excess of 340µmol/L (3, 6, 8, 17). SCr is

relatively reliable of representing actual renal function in patients with compensated cirrhosis however it performs far less adequately in decompensated cirrhosis owing to comorbid sarcopenia and the significant reduction in creatine to creatinine conversion within the liver and reduction in release from muscle mass (18). Herein, some decompensated cirrhotic patients may in fact have normal SCr despite significant acute renal failure (19). As such, patients with significant, albeit milder acute renal failure may not be appropriately diagnosed and managed until the nominal figure of 133µmol/L is reached to fulfil the ICA diagnostic criteria, exposing them to much severer acute renal failure before therapy is initiated. As such, a working party addressing renal dysfunction in cirrhosis have proposed new criteria for the diagnosis of AKI in cirrhosis in a bid to reduce morbidity and mortality and to improve treatment response (20). The group have proposed that a diagnosis of acute renal impairment and initial management thereof should be instituted in those patients experiencing a SCr increase >50% from baseline or >26.4µmol/L in a 48hour period without necessarily reaching a SCr of 133µmol/L. These criteria allow for earlier intervention in patients with a lesser degree of renal failure, likely improving the chances of a successful outcome.

Multiple studies have described a significant benefit of reduced mortality in patients for HRS in patients who responded to terlipressin therapy compared with placebo (3, 8, 16, 17). Neri et al demonstrated that the probability of survival was significantly higher in the subjects treated with terlipressin who had a response to therapy ($p<0.0001$), with one of only two predictors of survival on multivariate analysis being SCr reduction on therapy ($p<0.001$) (8). An alternate non-controlled study found response to terlipressin to be positively associated with 3 month survival compared with non-responders ($p=0.03$) with a significantly higher HRS reversal rate compared with a group of matched historical controls (17). An improvement in SCr not only demonstrates terlipressin response, but further, an increasing percentage

improvement of SCr on treatment is highly correlated with improved survival (21). The North American studies however failed to demonstrate a mortality benefit in patients treated with terlipressin compared with albumin therapy alone owing to a lack of a significant HRS reversal response rates between the two cohorts. However the cumulative responders (irrespective of treatment) had improved survival compared to non-responders in both studies (6, 16) which is unsurprising given reversal of HRS is associated with reduced mortality. Reduction in mortality in patients treated with terlipressin for HRS was recently addressed in a Cochrane review published in 2017 with data included from 9 large high quality RCTs and an analysis of 534 participants (22) – this demonstrated a reduction in mortality in patients with HRS treated with terlipressin compared with placebo/no intervention with a risk ration of 0.85 (95% confidence interval 0.73 to 0.98) and a number needed to treat for an additional beneficial outcome to prevent one death of 10.

Predictors of response to terlipressin for the management of HRS:

The above studies demonstrate that there is a wide range of response to terlipressin therapy. Multiple studies have tried to elicit predictors of response to terlipressin therapy. One such study (23) demonstrated on univariate and multivariant analysis that a lower baseline serum bilirubin was associated with response to terlipressin therapy - HRS reversal in patients treated with terlipressin was seen in 67% of participants with an initial serum bilirubin of <171µmol/L compared with only 13% in those participants with bilirubin >171µmol/L ($p<0.01$) (23). An increase in MAP at day 3 with >5mmHg was also demonstrated to be associated with increased likelihood of HRS reversal when treated with terlipressin – 73% of patients with >5mmHg increase in MAP achieved HRS reversal versus 36% in patients with <5mmHg increase ($P<0.05$) (23). A lower baseline creatinine was associated response to terlipressin therapy [247.5 vs 291.7µmol/L] ($p<0.05$) in addition to a range of

markers of less severe hepatic impairment including a lower INR, MELD and CP score ($p<0.05$) (17). A large analysis regarding predictors of response to terlipressin therapy for HRS suggests that the greatest benefit of terlipressin over albumin therapy alone was in patients with an initial SCr between 265µmol/L and 442µmol/L, where the absolute difference in reversal of HRS was 22% favouring terlipressin (24). The highest initial SCr in this group in which HRS reversal was achieved was 495µmol/L and the group suggested that treatment is likely futile with an initial SCr >618µmol/L. The authors do however reference a case in which a patient with HRS treated with terlipressin with an initial SCr of 734µmol/L achieved HRS reversal (4). A further study supported a lower baseline creatinine being associated with increased response to terlipressin therapy (13).

Terlipressin compared to ocreotide/midodrine for HRS

Terlipressin has also been demonstrated to be superior to alternate therapies for HRS commonly used in North America. Cavallin et al (9), conducted a prospective RCT comparing terlipressin therapy to combination midodrine and ocreotide, with both arms receiving daily albumin infusion. Forty-nine patients with HRS in keeping with the IAC diagnostic criteria were randomised to receive either terlipressin or ocreotide/midodrine. The terlipressin group (n=27) were commenced on 3mg daily infused over 24 hours, which could be incremented to a maximal dose of 12mg/day. The ocreotide/midodrine (n=22) were administered 100mcg/7.5mg TDS respectively which could be increased to a maximal dose to 200mcg/12.5mg TDS. These therapies were continued for an additional 24 hours beyond reversal of HRS (defined as creatinine < 133mmol/L) or a total duration of 14 days. The primary endpoint was defined as reversal of HRS which and was achieved in 55.8% of the terlipressin group compared with only 4.8% of the ocreotide/midodrine cohort ($p<0.001$).

Terlipressin vs Noradrenaline for HRS:

Noradrenaline (NA) is a catecholamine with predominantly alpha-adrenergic activity which has been shown to have a renal vasodilatory effect and improve renal blood flow (25, 26). As such it was postulated that it would have similar efficacy to terlipressin for the treatment of HRS. Following an initial small pilot trial, five prospective randomised open labelled studies have compared the efficacy of terlipressin with NA for the management of HRS. All have shown similar efficacy between the two therapies(27-32).

Sharma et al (27), performed an open label, randomised, controlled trial of NA compared with terlipressin for the treatment of Type 1 HRS. Forty consecutive patients were recruited with HRS and creatinine >221µmol/L. All patients underwent volume expansion with albumin 60 grams/d for 2 consecutive days and if urine output (UO) remained <600mls/day or SCr >133µmol/L they were randomised to treatment with terlipressin or noradrenaline. Group A (n=20) were commenced on NA 0.5mg/h with target to increase systolic blood pressure (SBP) by 10mmHg and UO to > 50mls/hr. If this was not achieved at 4 hours, NA was increased by 0.5mg/h to a maximum of 3mg/h. Group B (n=20) were commenced on terlipressin 0.5mg QID and were dose escalated by 0.5mg QID if SCr hadn't fallen by >88 µmol/L over a 3-day period. The groups were followed for 15 days. Both groups demonstrated a statistically significant improvement in SCr, serum sodium, creatinine clearance, mean urine output and mean MAP ($p<0.05$). Moreover there was no significant intergroup difference in these parameters nor was there any difference in survival at 15 days between the terlipressin and NA arms (group A 55% vs group B 55% $p=0.798$).

The comparative effect of NA on HRS was also demonstrated in a further open label RCT in India. Singh et al (28), randomised 46 patients into two groups to receive either terlipressin (n=23) or NA (n=23) in addition to 20g/day of albumin. The same dosing regimen and monitoring approach was utilised as per the previous study [9]. Irrespective of treatment arm, both groups achieved a significant reduction in SCr

and an increase in urine output and MAP without significant differences in benefit between the groups (p>0.05). Moreover, in concordance with the earlier RCT there was no difference in response to therapy (defined as creatinine <133µmol/l) between the terlipressin and NA groups (39.1 vs 43.3% respectively p>0.05) nor differences in survival at 15 days (39.1 vs 47.8% p=0.46). This study also demonstrated a significant cost reduction in regards to pharmaceuticals alone in the NA group compared with terlipressin (275 euro vs 975 euro p<0.05).

The five RCTs comparing NA and terlipressin for the management of HRS (27-31) reveal both therapies have similar efficacy and as such NA remains a suitable alternative to terlipressin when this therapy is unavailable or where patients need pressor support for circulatory failure. In patients who do not require intensive care then terlipressin has a clear advantage in that it can be safely administered in a hospital general ward without the requirement for intensive and invasive monitoring.

Terlipressin for the management of variceal bleeding

Terlipressin vs ocreotide in the management of variceal bleeding:

Terlipressin has been demonstrated to have greater efficacy in reducing oesophageal variceal pressure compared to ocreotide(33). In one study 27 patients were administered either a bolus of 2mg terlipressin, 50mcg ocreotide or distilled water IV in three treatment arms and pressure measurements were collected using a speciality endoscopic probe applied directly to the varix. There was a significant reduction in mean variceal pressure by 27% in the terlipressin group without significant change in the remaining groups (p<0.05).

An alternate study assessed the haemodynamic effects including MAP, heart rate, hepatic venous pressure gradient (HVPG) and portal venous flow assessed by duplex doppler ultrasonography at baseline and then 1, 5, 10, 20 and 25 minutes after

administration of IV boluses of terlipressin, ocreotide infusion or placebo(34). An infusion of 250mcg of ocreotide was associated with a rapid significant reduction in HVPG and PVG at 1 minute ($p<0.05$) however pressures measurements had returned to baseline valves at all other subsequent time points. Conversely, Terlipressin administration was associated with a significant decrease in HVPG and portal venous flow which was sustained at all time-points ($p<0.05$).

Multiple smaller prospective, placebo controlled RCTs have demonstrated terlipressin to be superior to placebo regarding likelihood of active variceal bleeding at index gastroscopy, reduced re-bleeding rates and reduced transfusion requirement (35-37) however these studies predated modern band ligation techniques now used as standard of care in variceal haemorrhage.

With this early data suggesting a greater effect of terlipressin over octreotide at reducing variceal pressure several studies have attempted to demonstrate this benefit on clinically significant end-points (38-42). A recent, large RCT assessed the outcomes of patients presenting with variceal bleeding with adjuvant treatment with either terlipressin, somastostatin or ocreotide (43). 780 patients presenting with variceal haemorrhage were enrolled across 11 Korean centres and were commenced on either Terlipressin [2mg bolus then 1mg QID for five days] (n=261), somatostatin [250mcg bolus then 250mch/hr for five days] (n=259) or octreotide [50mcg bolus then 25mcg/hr]. At the time of the index gastroscopy there was no significant difference in active bleeding rates between the three treatment arms (46.0%, 46.2% and 46.5%) nor between rates of bleeding control without rescue therapy (balloon tamponade, TIPSS) (89.7%, 87.6% and 88.1% $p=0.752$). In addition there was no significant difference in rates of re-bleeding within the 5-day treatment period between the three therapies nor in mortality rates.

A second double-blind RCT explored whether there were differences in clinical outcomes between terlipressin and ocreotide therapy in patients presenting with variceal bleeding (44). In this study 324 patients were randomised to either

terlipressin or octreotide in addition to standard endoscopic therapy. The only significant difference demonstrated was that patients treated with terlipressin were less likely to have active bleeding at the time of index gastroscopy (16% vs 25.5% respectively p=0.034). However there were no significant differences in other clinical outcomes including mortality.

Despite improved portal hemodynamics with terlipressin compared to ocreotide, the only significant benefit of terlipressin identified in trials exploring its role in acute variceal bleeding is active bleeding at time of index gastroscopy, while re-bleeding and mortality rates are unchanged. The standard of care for acute variceal bleeding remains pharmacological therapy (with either octreotide or terlipressin) in combination with endoscopic variceal band ligation. There remains little doubt that terlipressin exerts a greater physiological effect on variceal pressure compared with octreotide. The explanation as to why this doesn't translate into any clinically significant benefit over octreotide in patients presenting with variceal bleeding likely lies with the fact that most of the efficacy of therapy resides with EVBL with a relatively small additional component from the pharmacological therapy.

Terlipressin's effect on serum sodium concentration

While terlipressin is largely used for its activation of the V1a receptor, it is also recognised that terlipressin also causes activation of the V2 renal receptors (45). Stimulation of the V2 receptor leads to an increase in aquaporin 2 in the renal collecting duct and thus increased solute free water absorption and can potentially resultant in hyponatraemia (45).

There have been multiple publications that have explored the effect of terlipressin on serum sodium concentrations (45-49) including several that describe neurological complications from profound hyponatraemia (50-52). Most publications describe hyponatraemia as a complication of terlipressin usage whilst a retrospective

Australian study reported the beneficial effect of terlipressin usage in conjunction with albumin infusion for the treatment of clinically significant hyponatraemia.

One large retrospective study described the effect of terlipressin on serum sodium in 58 patients with portal hypertension and gastro-oesophageal variceal bleeding (47). All were treated with terlipressin 2mg 4 hourly initially and then subsequently reduced to a dose of 1mg 4 hourly after 24hr for a total of 5 days. Across this population of patients mean sodium fell from 134.9 ± 6.6mmol/L at day one to 130.5 ± 7.7mmol/L at day 5 of treatment (p=0.002). There was significant variation in the magnitude of the fall in sodium. In 19 patients it was <5mmol/L, 18 patients: 5-10mmol/L (n=18, 31%) and in 21 patients serum sodium fell by >10mmol. Three of the 21 patients (14%) who experienced a decrease in sodium >10mmol/L had neurological sequelae including altered conscious state, coma and in once instance seizures complicating osmotic demyelination in the setting of rapid correction of serum sodium. In 95% of cases, hyponatraemia resolved with withdrawal of terlipressin. Importantly this population was compared to 174 contemporary patients treated with somatostatin for variceal bleeding where no change in serum sodium was observed during 5 days of therapy.

These findings are supported by a recent large retrospective study that documented the risk of hyponatraemia when terlipressin is utilised for GI bleeding (53). Of the 151 patients in the series treated with terlipressin, 66.9% had a reduction in serum sodium of >5mmol/l and 38.5% had reduction of >10mmol/l. In most cases cessation of terlipressin resulted in rapid correction of serum sodium. Baseline serum sodium was also identified as a significant determinant in an alternate prospective study(49).

These publications contrast with an Australian study that described terlipressin as an effective therapy for profound hyponatraemia in cirrhotic patients (46). This groups retrospective case series described 23 cirrhotic patients who were commenced on terlipressin for the indication of hyponatraemia unresponsive to fluid restriction and diuretic cessation. These patients were compared to 11 decompensated cirrhotic

with hyponatraemia managed with fluid restriction and albumin infusion alone. The dosage of terlipressin was between 0.5-1mg 4 hourly for all patients and they received albumin infusion 40 grams daily. At 7 days, there was a significant increase in sodium from 120 mmol/L to 129 mmol/L ($p<0.05$) compared to no change in the albumin infusion only group at 123 mmol/L at baseline and remaining unchanged at day 7 ($p>0.05$). Forty-eight per cent (11/23) of the patients in the terlipressin group were able to recommence diuretics on terlipressin for the management of problematic fluid overload. The group postulated that the combination of albumin infusion in addition to terlipressin helped to augment the renal response to terlipressin increasing serum sodium. On multivariate and univariate analysis the utilisation of terlipressin was the only factor leading to resolution of hyponatraemia.

The contrasting conclusions of these papers that explore the effect of terlipressin use on serum sodium need analysis. It is likely that the explanation for the disparate results relies on whether albumin was used in conjunction with terlipressin or not. The papers that described terlipressin causing hyponatraemia did not use albumin as part of the routine therapy whereas the Australian paper describing terlipressin as an effective therapy for hyponatraemia did. Albumin infusion results in an increase in effective blood volume. This in turn leads on to decreased baroreceptor activation and reduced AVP release and water retention. Thus albumin induced reduction in AVP production overrides the terlipressin induced V2 receptor stimulation with the net effect being positive free water clearance. Prescribing clinicians need to be mindful of terlipressin induced hyponatraemia. Profound and life-threatening hyponatraemia can result from this medication's use and, as such, patients need to be carefully monitored. When clinically significant hyponatraemia results albumin therapy should be instituted or terlipressin therapy should be withheld.

<u>Continuous versus bolus Terlipressin for HRS:</u>

The current standard practice for terlipressin administration is that it is given by bolus doses every 4-6 hours when used for either portal hypertensive bleeding or HRS (54). However, the haemodynamic effect of terlipressin on portal pressure has been shown to last no more than 3-4 hours (55). This raises the question as to whether terlipressin administered by continuous infusion may have greater efficacy then standard bolus dose administration. Recently important clinical data has been published comparing the two methods of administration.

The haemodynamic effects of either bolus or terlipressin infusion has been examined in a small cohort of patients undergoing TIPSS for the management of variceal bleeding or Budd-Chiari syndrome (56). In total 21 patients had TIPSS performed with a pressure catheter placed within the portal vein post TIPSS insertion. Ten patients received a 1mg terlipressin bolus followed by 4mg infusion over 24 hours while the conventional intermittent bolus group received a 2 mg bolus initially and then 1mg four hourly. In the group who received bolus dose terlipressin a portal venous pressure fall >20% from baseline was observed for only 4 hours out of the total 24 hours of the study period. This contrasted sharply with the continuous infusion group. In the latter group portal pressure reduction >20% from baseline was maintained throughout the 24 hour monitoring period. Assessing area under the curve, there was a statistically significant reduction in portal pressures in the infusion group compared with the bolus group over the 24 hour study period ($p>0.05$).

It was postulated from a small retrospective study that when applied clinically this would lead to a reduction in 24 hour dosage requirement and reduced adverse effects (57). A important prospective RCT was recently published exploring improved safety and efficacy when terlipressin was given by infusion versus bolus dose terlipressin in patients with HRS (58). In this study 78 patients with HRS were randomly assigned to a continuous infusion of terlipressin at 2mg/day or bolus doses starting at 0.5mg 4 hourly and dose escalated if there was an inadequate response.

Response to treatment was assessed in both groups at 48 hour intervals and if SCr had decremented <25%, the amount of terlipressin was gradually increased to a maximum of 12 mg/day in both groups. Both groups received standard doses of albumin. Terlipressin was continued until resolution of HRS 1 (creatinine <133µmol/L), liver transplantation, death or to a maximal duration of 15 days. The primary end point was the prevalence of drug-related adverse events while secondary end point included response to treatment (complete response defined as creatinine <133µmol/l and partial response a >50% reduction in SCr) and 90-day transplant free survival. 34 patients were randomised to infusion administered terlipressin and 37 to bolus administration. The study revealed significantly fewer adverse events in the infusion group compared to those receiving the drug by bolus administration. Overall total adverse events were seen in 35% of those receiving the drug via infusion compared with 62% via bolus administration ($p<0.025$). Severe adverse events were also less frequent in the infusion group (21% vs 43%, $p<0.05$). Interestingly the 6 patients in the terlipressin bolus group who experienced severe adverse events were commenced on salvage infusion based terlipressin at an initial dose of 2mg over 24hours. All 6 patients tolerated infusion administered terlipressin and all experienced complete response with creatinine <133mmol/L (3 patients at a dose of 2mg/24hr, and 3 at 4mg/24hr). There was no statistically significant difference in the number of patients experiencing complete response to treatment between the two groups (infusion group 64.85% vs bolus group 76.47% $p>0.05$). There was no significant difference in the mean reduction of creatinine nor the mean time to achieve treatment response however the maximal and mean dose of terlipressin required to achieve response was lower in the infusion vs bolus administered group (2.23+/-0.65mg vs 3.51+/-1.77mg p=.0001). There was no difference in transplant free survival between the cohorts.

These important but preliminary studies suggest that there may be significant clinical differences in the safety and perhaps efficacy depending on the method of

terlipressin administration. Further studies are needed to confirm these findings in patients with HRS and also in patients with variceal bleeding.

The use of ambulatory terlipressin infusion:

There is a population of patients who are awaiting liver transplantation who have terlipressin responsive HRS. For many patients in this group attempts to wean terlipressin are met with recurrence of HRS. For this cohort of patients the options are thus to remain on terlipressin until transplanted or to develop renal failure and commence renal replacement therapy. In this group of terlipressin "dependent" patients many may need the drug for months until a suitable organ becomes available for transplantation. This long time course of therapy has led to the initiation of programmes that aim to deliver continuous terlipressin infusions in an ambulatory outpatient setting.

A case report from our own unit describes a 59 year-old gentleman with Child-Pugh C cirrhosis complicated by encephalopathy, diuretic refractory ascites and hepatocellular carcinoma who was successfully bridged to transplantation with hospital-in-the-home based terlipressin infusion for the management of HRS Type 1(59). The patient had two acute admissions in the preceding months with SCr >400µmol/L which had been responsive to bolus dose terlipressin. He was commenced on terlipressin 3.0mg/day via 24hr infusion with complete normalisation of his renal function. Hospital in the home nurses attended to the patient on a daily basis to ensure clinical stability and replace the 24hour infusion. No terlipressin related adverse events were encountered during his 22 days of ambulatory therapy and his HRS remained terlipressin responsive.

In a subsequent series we have described six patients with HRS as defined by IAC who were successfully managed with ambulatory terlipressin infusions (60). In all cases patients received intermittent bolus administration of 0.85mg as an inpatient for a mean of 6 days to confirm efficacy and tolerability before being transitioned to

a 3.4mg/24hrs via a peripherally inserted central catheter infusion line. Two patients later tolerated a dose reduction to 1.7mg/24hrs without recurrence of HRS. Three patients were bridged to OLT with a mean of 21 days (range 1-37), one patient achieved reversal of HRS and remained stable without terlipressin after successful hepatitis C eradication therapy. The two remaining patients had their infusions ceased. One patient due to ongoing bleeding at a peripherally inserted central catheter infusion site while the other patient was deemed inappropriate for transplantation**. There was significant cost savings associated with the transfer of the care from the hospital to the hospital-in-the-home service.

The experience at this transplant centre suggests that in carefully selected patients, the use of ambulatory terlipressin infusion is a safe, efficacious and well tolerated therapy for the management of HRS 1 as a bridge to transplant allowing patients to be managed beyond the confines of an inpatient ward.

Diuretic refractory ascites

The use of outpatient terlipressin infusion for the management of diuretic refractory ascites has been investigated in one small single centre pilot study (61). Five patients were included in the study. All were Child Pugh C with a mean MELD score of 18. All five patients were undergoing weekly or fortnightly paracentesis for diuretic refractory ascites prior to enrolment. The five patients were commenced on a terlipressin infusion 3.4mg/24hr via a peripherally inserted central catheter and followed for 4 weeks. The patients served as their own controls with parameters from the 4 weeks prior to the terlipressin infusion compared with the 4 weeks on therapy. Compared to the observation period there was a significant reduction in volume of ascites drained during the treatment period (22.9 vs 11.9L $p<0.05$) with two patients requiring no further paracentesis whilst on terlipressin therapy. There was a reduction in the number of paracentesis required (3.2 vs 2.2 $p<0.05$) over the

treatment period as well as an increase in 24hr urinary sodium excretion (88.3 vs 153.4mmol/day $p<0.05$).

Conclusion

The unique pharmacological effects of terlipressin on the cirrhotic circulation are to reduce portal pressure and increase renal blood flow. These effects have been exploited in studies exploring its role in the management of HRS and variceal bleeding. Over more recent years as the physiological effects of terlipressin have become better understood roles for the drug in the setting of refractory ascites and cirrhotic hyponatraemia have been proposed. In addition to its potentially expanded indications the use of terlipressin as a continuous infusion rather than bolus administration and use in the outpatient setting has seen a reinvigoration in research and publications for this therapy. With a drug that has been available for more than 20 years one might expect that clinical interest in the therapy may be diminishing. However the opposite appears to be the case with terlipressin. There are currently there are more than 50 ongoing clinical studies exploring further expansion of the role of this medication. For clinicians involved in the management of patients with advanced liver disease terlipressin plays a central role in the management of complications and is likely to play an expanded role in years to come.

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	Type of study	Number of participants	Type HRS	ICA HRS criteria met	Albumin (grams/day)	Treatment arm	Mean SCr Baseline (µmol/L)	Mean SCr change (µmol/L)	HRS reversal (SCr < 133 µmol/L)	Survival	Maximal treatment duration (days)	Maximal terlipressin dosage	Alternate vasoactive drugs
Uriz et al, 2000 (4)	Case series	9	1 / 2	Yes	20-40	Terlipressin	345	- 212	78%	NA	15	2mg Q4H	Nil
Solanki et al, 2003 (3)	RCT	24	1	Yes	20	Terlipressin	256	- 150 #	42%	D15 41% #	15	1mg Q12H	Dopamine
						Placebo	194	+ 150	0%	D15 0%			
Neri et al, 2008 (8)	RCT	52	1	Yes	20-40	Terlipressin	248	- 136 #	80% #	D180 42% #	19	1mg Q8H	Nil
						Placebo	256	- 68	19%	D180 16%			
Sanyal et al, 2008 (6)	RCT	112	1	Yes	25	Terlipressin	350	- 62 #	34% #	D180 43%	14	2mg Q6H	Nil
						Placebo	340	+ 36	13%	D180 37%			
Boyer et al,	RCT	196	1	Yes	20-40	Terlipressin	318	- 97 #	NA	D90 58%	14	2mg Q6H	Nil

2016 (16)						Placebo	327	- 53	NA	D90 55%			

Table 1: Key studies determining the benefit of Terlipressin for Hepatorenal Syndrome

# $p < 0.05$