

**Worsening of cerebral hyperemia by the administration  
of terlipressin in acute liver failure  
with severe encephalopathy following terlipressin**

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## ABSTRACT

There is increasing evidence that terlipressin is useful in patients with cirrhosis and hepatorenal syndrome, but there are no data of its use in patients with acute liver failure (ALF) in whom hepatorenal syndrome is common. Although terlipressin produces systemic vasoconstriction, it produces cerebral vasodilatation and may increase cerebral blood flow (CBF). Increased CBF contributes to intracranial hypertension in patients with ALF. The aim of this study was to evaluate the safety of terlipressin in patients with ALF with respect to cerebral haemodynamics. Six successive patients with ALF were electively ventilated for grade IV hepatic encephalopathy. Patients were monitored invasively and CBF was measured (Kety-Schmidt technique). Measurements were made before, at 1, 3 hour and 5 hours after intravenous (single bolus) administration of terlipressin (0.005 mg/kg) intravenously (single bolus), median 0.25mg (range 0.2-0.3). There was no significant change in heart rate, mean arterial pressure or cardiac output. CBF and jugular venous oxygen saturation both increased significantly at 1 hour ( $p < 0.00016$ ) respectively. Intracranial pressure increased significantly at 21 hours ( $p < 0.031$ ), returning back to baseline values at 42 hours. This study shows that administration of terlipressin, at a dose that did not alter systemic haemodynamics hemodynamics, resulted in worsening of cerebral hyperemia and intracranial hypertension in patients with ALF and severe hepatic encephalopathy. These data suggest the need to exercise extreme caution in the use of terlipressin in these patients in view of its potentially deleterious consequences on cerebral haemodynamics.

## INTRODUCTION

Acute liver failure (ALF) is characterised characterized by rapid deterioration in the level of consciousness, and a mortality rate of about 90% in patients who fulfill criteria for poor prognosis.<sup>1</sup> In the later stages of encephalopathy, elevation in intracranial pressure (ICP) is common due to the development of cerebral oedema edema. The exact pathogenic mechanism of the increased ICP is unknown but current literature suggests pports a two-multiple hit hypothesis in which ammonia is thought to be central; a central role for ammonia with a later increase in cerebral blood flow (CBF) accentuating the rise in ICP.<sup>2-4</sup> Studies in a portacaval shunted rats administered an ammonia load have demonstrated a rise in CBF that paralleled the increase in ICP and correlated directly with the brain water content.<sup>5,6</sup> In the later stages of ALF, but before intracranial hypertension is manifest, cerebral hyperemia often prevails and seems to precede herniation.<sup>7,8</sup> Cerebral hyperemia is therefore of crucial importance in the development of increased ICP in ALF.

Normal cerebral vascular resistance is essential for the maintenance of cerebral autoregulation. Reactive vasodilatation or vasoconstriction ensures constant cerebral perfusion.<sup>9</sup> In patients with ALF, autoregulation is impaired, but can be restored if cerebral arteriolar tone is increased by hyperventilation, suggesting that cerebral vasodilatation is responsible for the impairment in autoregulation.<sup>5,10</sup> In patients with ALF, a reduction in CBF results in a decrease in ICP.<sup>11</sup>

The mechanism of the increased CBF has to be examined in relation to the generalized circulatory disturbance which is characterised by tachycardia, hypotension, increased cardiac output and peripheral vasodilatation which may contribute to the occurrence of hepatorenal syndrome in ALF. Hepatorenal syndrome develops in approximately 55% of all patients referred to specialized units with ALF

and frequently these patients require renal support. <sup>126-8</sup> - 14

Terlipressin, is an inactive vasopressin analogue, which is slowly metabolized in vivo to its active form, lysine vasopressin. It has been used to treat norepinephrine-resistant hypotension when associated with septic shock <sup>9</sup> and there is an increasing body of evidence that it may be useful in patients with cirrhosis and hepatorenal syndrome. <sup>10-14</sup>

has been used to treat norepinephrine-resistant hypotension when associated with septic shock <sup>15</sup> and there is an increasing body of evidence that it may be useful in patients with cirrhosis and hepatorenal syndrome.<sup>16-20</sup> Vasopressin is a potent systemic vasoconstrictor, thought to exert its effects through peripheral V1 receptors. In animal studies, the administration of vasopressin however, also increases CBF by dilating cerebral arteries.<sup>15-17,21-23</sup> Vasopressin may also regulate regional CBF by two balancing the effects of increased flow mediated by nitric oxide release from the endothelium, and with decreased flow in vessels contracted by direct stimulation of smooth muscle. <sup>2184</sup> It has been postulated that the increase in CBF may be mediated through cerebral V2 receptors. <sup>19</sup> In a preliminary report, vasopressin administration in an animal model of ALF and cerebral oedema edema resulted in worse brain swelling.  
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As hepatorenal syndrome and systemic hypotension are common in patients with ALF, terlipressin may be a useful drug for the management of these complications. However, given the distribution of the vasopressin V2 receptors in the brain it is possible that terlipressin may accentuate cerebral hyperemia and worsen intracranial hypertension in ALF. Our justification for aims in performing this small study was ere to evaluate whether terlipressin has any deleterious effect on cerebral haemodynamics prior to proceeding to a conducting a suitable randomized controlled trial of the use of terlipressin in patients with hepatorenal syndrome in ALF. In this study, we evaluated

the effect of administration of terlipressin at a sub-therapeutic dose to patients with ALF and Grade IV hepatic encephalopathy and measured serial changes in systemic haemodynamics, ICP and CBF.

## **METHODS**

Studies were undertaken at The Transplant Unit at the Royal Infirmary of Edinburgh between June and December 1999. with the approval was obtained of by the local Lothian Research Ethics Committee and written informed consent assent was obtained from the next of kin of each patient in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

**Study Design.** Six successive unselected patients with ALF were enrolled into the study with ALF. Patients had been admitted to the Intensive Care Unit with Grade IV hepatic encephalopathy were included into the study. and had cardiovascular and ICP monitors inserted. Patients were excluded if they required inotropic support or any specific treatment for elevated ICP prior to entry into the study. Cardiovascular haemodynamics, ICP, jugular venous oxygen saturation (JVOS), CBF and blood gases were measured prior to and then for 5 hours after administration of 0.005 mg/Kg of terlipressin [median 0.25 mg (range 0.2 - 0.3 mg)] as a single intravenous bolus (terlipressin acetate injection, Ferring Pharmaceuticals). This low dose was chosen to prevent significant changes in the systemic haemodynamics so as to allow assessment of changes in CBF irrespective of the changes in MAP.

**Patients.** We studied 6 patients with ALF (median age, 27 (22-46) years, 4 females, etiology: paracetamol~~acetaminophen~~: 4, acute fatty liver of pregnancy: 1: 1, non A, non B viral: 1: 1) and 4 fulfilled the Kings College Criteria for poor prognosis.<sup>1</sup> The median concentration of serum bilirubin was 156 ([range 102-345])  $\mu$ mol/L, prothrombin time 67 (range [49-123]) sec, plasma lactate 4.5 (range [2.9- 6.9]) mmol/L, arterial ammonia 212 ([167-311])  $\mu$ mol/L and the arterial pH was 7.32 ([7.20-7.43]). Median serum creatinine was 312 (range [189-365])  $\mu$ mol/L and 4 patients required renal support with continuous veno-venous haemofiltration for hepatorenal syndrome. Haemofiltration was started prior to and continued throughout the duration of the study.

**Monitoring and Measurements.** All the patients were mechanically ventilated following sedation with propofol. ICP was continuously monitored in 5 of the patients using a subdural fibre-optic system (Camino, Camino Laboratories, San Diego, USA). The

ICP value recorded was the at value obtained was recorded at hourly intervals. Cardiovascular haemodynamics were monitored continuously with a Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA). Heart rate, MAP and cardiac output were recorded at hourly intervals.

**Measurement of cerebral blood flow and jugular venous oxygen saturation.** In

order to measure cerebral blood flow (CBF), an arterial catheter was inserted into the femoral artery and a jugular bulb catheter was inserted into the left internal jugular vein (4F Opticath, U440, Abbot, USA). Correct positioning of the jugular bulb catheter was confirmed with a lateral head and neck radiograph.<sup>2620</sup> Cerebral venous monitoring via a jugular bulb catheter allows assessment of global oxygen delivery adequacy and does not exacerbate intracranial hypertension.<sup>2127</sup> Jugular venous oxygen saturation (JVOS) was monitored continuously via the reverse jugular catheter and recorded hourly. CBF was only determined if the patient was hemodynamically stable, defined as a difference variation of less than 10% in the mean arterial pressure. Ventilation was adjusted to achieve an arterial carbon dioxide tension of 4-4.5 kiloPascals (kPa), and was not altered again during the study to prevent PaCO<sub>2</sub> becoming a confounding factor of CBF. Modification of the Kety-Schmidt technique<sup>2822</sup> was used to measure CBF which is dependent on the rate of uptake of nitrous oxide by the brain as detailed previously.<sup>239</sup> \_Measurements were made prior to and then after 1 and 5 hours following the administration of terlipressin.

**Statistics.** Data are expressed as median and range. Differences in measured variables over between individual time points for acid base status and systemic haemodynamics after administration of terlipressin was calculated using the Wilcoxon Signed Rank test, a one-way ANOVA with Bonferroni post correction. Significance was accepted at p<0.05. Differences in the cerebrovascular haemodynamics were also calculated using



the Wilcoxon Signed Rank test.using repeated measures one-way ANOVA with Bonferroni post correction.

## RESULTS

**Patients.** Three of the four patients who fulfilled criteria for poor prognosis, underwent

successful OLT a median of 46 ([37-67]) hours after admission to the intensive care unit. The 4<sup>th</sup> patient, who had psycho-social psychosocial contraindications to OLT, died 4 days after admission to the intensive care unit with multiorgan failure. The other two patients recovered without need for OLT and could be discharged from the intensive care unit 73 and 84 hours, respectively, after first presentation with Grade IV encephalopathy.

**Cardiovascular Haemodynamics.** As shown in Table 1, all patients showed evidence of a hyperdynamic circulation with increased cardiac output and heart rate and reduced MAP and systemic vascular resistance. Following administration of terlipressin there was minimal increase in the MAP (Figure 1a) and systemic vascular resistance and, an insignificant reduction in cardiac output and heart rate, but none of these changes were either clinically or statistically significant. An increase in hydrogen ion concentration was found to be significant at 5 hours following terlipressin (p=0.031), though this corresponds to a change in arterial pH from 7.41 to 7.39, which was not thought to be clinically relevant as both values remain within normal limits. There were no other significant changes in the central venous pressure or the arterial blood gases found (Table 1).

**Cerebrovascular Haemodynamics.** There was a significant increase in CBF from a median of 69 ([range 48-83]) ml/100g/min to 81 (range [62-97]) ml/100g/min (p

<0.001=0.016), 1 hour after administration of terlipressin (Figure 1c). The values CBF remained significantly higher at 3 hours following terlipressin administration, but at returned to baseline values at 5 hours after terlipressin administration were similar to had returned to baseline values; 70 (53-95) ml/100g/min. This was associated with an increase in ICP in all patients from a median of 15 (range [13-18]) mmHg to 20 (range [16-23]) mmHg (p=0.031<0.01) after 1 hour, becoming maximal at 2 hours with median of 22 (range 15-23) mmHg ( $p<0.001$ ). The rise in ICP remained significant at 3 hours, with median 18 (14-23) (Figure 1b), returning to baseline values at 4 hours. In keeping with the increased CBF, the JVOS increased from a median of 75% (range [67-89]) to 87% (range [75-94]) (p=0.016<0.001) 1 hour afterwards and remained significantly elevated high but returned to values that were similar to the baseline values by for 3 hours, returning, returning to baseline values at 5 hours 80% ([66-90]) (Figure 1d).

## **DISCUSSION.**

This study demonstrates that administration of low dose terlipressin produces no significant changes in systemic haemodynamics, but is associated with increases in CBF and a resultant increase in ICP, suggesting the need for extreme caution in the use of this drug in patients with ALF and with grade IV hepatic encephalopathy.

Increased ICP and brain herniation is a major cause of mortality in patients with ALF if this is not controlled by repeated mannitol treatments and ultrafiltration.<sup>1</sup> Although the pathogenesis of increased ICP in ALF is not entirely clear, At the time this study was planned (1998), there was increasing concern that increased CBF may underlie the pathogenesis of increased ICP in patients with ALF. In particular, data from Aggarwal et al. <sup>24</sup> showed that those patients with high ICP have elevated CBF. Since then, there has been is an increasing body of literature suggesting a crucial role for cerebral hyperemia as being critical in the development of intracranial hypertension in ALF. Data supporting the above are derived from observations in

experimental animals <sup>2,3,5,6</sup> and also from studies in patients with ALF. Studies in portacaval shunted rats administered an ammonia load have demonstrated a rise in CBF that paralleled the increase in ICP and correlated directly with brain water content. <sup>25,26, 26</sup> Cerebral hyperemia is of crucial importance in the development of increased ICP in ALF. Normal cerebral vascular resistance is essential for the maintenance of cerebral autoregulation. Reactive vasodilatation or vasoconstriction ensures constant cerebral perfusion.<sup>27</sup> When modalities are introduced to control the rise in CBF, such as methionine-sulfoxamine (an inhibitor of glutamine synthase) <sup>25</sup> and mild hypothermia <sup>28</sup>, ammonia-induced cerebral edema is prevented. It has also been shown that the cerebral vasoconstrictor, indomethacin, blunts the rise in CBF in portacaval shunted rats receiving an ammonia load and that the consequent reduction in CBF leads to a disproportionate reduction of ammonia uptake by the brain which may reduce brain edema. <sup>29</sup>

<sup>7, 10,30,31</sup> Experiments in portacaval shunted rats given ammonia infusion develop cerebral oedema~~edema~~ which is preceded by increases in CBF.<sup>5,6</sup> Furthermore, the rise in ICP parallels the increase in CBF. When modalities are introduced to control the rise in CBF, such as methionine-sulfoamine (an inhibitor of glutamine synthase) <sup>5</sup> and mild hypothermia <sup>32</sup>, ammonia -induced cerebral oedema~~edema~~ is prevented. It has also been shown that the cerebral vasoconstrictor, indomethacin, blunts the rise in CBF in portacaval shunted rats receiving an ammonia load and that the consequent reduction in CBF leads to a disproportionate reduction of ammonia uptake by the brain which may reduce brain oedema~~edema~~. <sup>33</sup> Direct evidence for the role of cerebral hyperemia being important in the pathogenesis of increased ICP has been derived from studies in patients with ALF, that have shown that an increase in CBF, induced by an increase a rise in MAP, was associated with an

increase in ICP.<sup>33,34</sup> The rise in ICP did not occur if the cerebral hyperemia was prevented from occurring using hypothermia.<sup>11,30,31,314</sup> Although data in humans are variable, they support the notion that increased CBF is crucial in the pathogenesis of increased ICP.<sup>5,7,8,10,30,31,343</sup> Indeed, in the present study the increase<sup>rise</sup> in CBF induced by terlipressin resulted was associated inwith an increase in ICP.

The loss of CBF autoregulation is likely to be mediated through cerebral vasodilatation.<sup>354</sup> However, the increase in CBF following administration of terlipressin is unlikely to have occurred due to a loss of reflect the effects of altered CBF autoregulation because administration of terlipressin was not associated with any significant changes in the mean arterial pressure and therefore cerebral perfusion pressure. In addition, the effects of a low dose bolus of terlipressin on CBF and consequent ICP were of short duration and completely reversible, with all values returning to baseline values at 5 hours which is entirely consistent with the pharmacokinetics of terlipressin which has a half-life of 50 minutes.<sup>35</sup>

The exact mechanism by which terlipressin leads to an increase in CBF cannot be elucidated from this study but we postulate that it is likely to be mediated through cerebral V2 receptors. If the effect had been preferentially mediated through V1 receptors, then we would have expected a rise in MAP due to its peripheral vasoconstrictor effects, which was not the case in this study. The results of a recent study by Chung et al.<sup>36</sup> using an experimental animal model of cerebral edema (ammonia infusion following portacaval anastomosis), demonstrated that vasopressin administration results in an increase in CBF and worsening of brain edema support this suggestion. They observed an increase in CBF when vasopressin was administered both in the presence of V1 and V2 receptor antagonists. With V1 receptor antagonism the increase in CBF following vasopressin occurred without a

simultaneous increase in the MAP indicating a V2 receptor dependent mechanism, as was observed in our study. Importantly, they also observed that the animals that were treated with vasopressin had higher ammonia concentrations. Although the exact mechanism of this hyperammonemia is not clear, it may represent reduced perfusion of critical ammonia removing organs.

In addition, the effects of a low dose bolus of terlipressin on CBF and consequent ICP were of short duration and completely reversible, with all values returning to baseline values at 5 hours which is entirely consistent with the pharmacokinetics of terlipressin with a half-life of 50 minutes.<sup>36</sup>

Evidence for increased brain nitric oxide in ALF exists in studies of animal models of ALF, where enhanced brain flux of nitric oxide has been demonstrated through increased expression of neuronal nitric oxide synthase.<sup>37</sup> It has been shown in rats that the increased brain uptake of L-arginine resulting from portacaval shunting results in a 2 fold increase in neuronal nitric oxide synthase protein expression and a concomitant 2.4 fold increase in neuronal nitric oxide synthase messenger RNA.<sup>38</sup> Increased neuronal nitric oxide synthase activity in the brain and the resulting nitric oxide production could contribute to the increased CBF.

In conclusion, the results of this study suggest that administration of even a single sub-therapeutic dose of terlipressin to patients with ALF and grade IV hepatic encephalopathy may have deleterious consequences through worsening of cerebral hyperemia and intracranial hypertension. The effect of terlipressin on CBF in patients with ALF and low -mild grade hepatic encephalopathy however, cannot be ascertained from the results of this study. Consideration of these findings suggests that it is unwise proceed with the use of terlipressin in a large scale clinical trial at this time. Thisese data suggests that extreme caution should be exercised and close monitoring

is required if this drug is used in patients with ALF and severe hepatic encephalopathy.



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## **LEGENDS TO FIGURE**

**Figure 1.** Changes in (a) mean arterial pressure (MAP); (b) intracranial pressure (ICP); (c) cerebral blood flow (CBF); and (d) jugular venous oxygen saturation (JVOS) prior to and after administration of 0.005 mg/Kg of terlipressin intravenously.

Individual patients are represented: Patient 1 represented by filled diamonds (◆, (◆); patient 2( by open squares (□); patient 3 by filled triangles (▲); patient 4 by filled squares( ■); patient 5 filled circles( ●); and patient 6 open circles( ○). P-values were calculated using the Repeated repeated measures one\_ way ANOVA with a Bonferonni post test Bonferonni correction. Wilcoxon Signed Rank test. ([Normal values (used by authorsauthor's institution)]); MAP 93 - 100 mmHg, CBF 45 - 50 ml/100g/min, ICP 0 -15 mmHg, JVOS 55 -75 %).

**Table 1. Acid-base status and Systemic haemodynamics after administration of 0.005 mg/Kg of Terlipressin intravenously.**

	<b>Pre</b>	<b>30 min. after terlipressin</b>	<b>60 min after terlipressin</b>	<b>5 hours after terlipressin</b>
Hydrogen ion concentration (mmol/L)	39.1 (37-42)		40.0 (38-43)	43.1 (37-45)
pCO <sub>2</sub> (kPa)	4.5 (3.9-4.7)		4.4 (4.0-4.5)	4.5 (4.2-4.6)
pO <sub>2</sub> (kPa)	13.1 (11.2-16.1)		12.9 (11.1-17.0)	11.7 (10.9-16.3)
Heart Rate (/min)	94 (73-103)	91 (73-108)	90 (73-103)	93 (77-99)
Cerebral perfusion pressure (mmHg)	63 (56-66)		61 (53-66)	64 (52-68)
Central venous pressure (mmHg)	12 (8-14)	11 (9-14)	11 (9-15)	10 (9-13)
Cardiac Output (L/min)	10.7 (8.8-13.1)	10.3 (9.1-12.9)	10.2 (9.1-12.8)	10.6 (8.8-13.0)
Systemic vascular resistance (dyn.sec/cm <sup>5</sup> )	464.8 (389-627)	502 (396-691)	485.6 (418-641.7)	502 (402-628)

Data expressed as median (range). None of the changes are statistically significant using one-way ANOVA with Bonferroni correction

