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Correspondence

Baclofen overdose

The recent case report, "Massive baclofen overdose", by Cooper DJ *et al*,[1] deserves some comment. We recently treated a 13 year old female with an overdose of 2500 mg of baclofen. She presented with coma, hypotension, hypotonia, hyporeflexia, but intact brain stem reflexes. She was treated with fluid and adrenaline infusions, making an uneventful recovery after 24 hours. The patient did receive a dose of midazolam in the Emergency Department for facial dystonia or twitching. The midazolam worsened the twitching and was not continued. An EEG revealed no evidence of seizure activity.

Several features of baclofen overdose should be clarified. Firstly, baclofen is a pre-synaptic GABA agonist with effects that are potentiated by benzodiazepines (e.g. clonazepam, midazolam and diazepam). The infusion of clonazepam 23 mg over 24 hours would clearly potentiate baclofen effects and may well have contributed to the patients prolonged coma. Secondly, the feature of facial twitching is an acute dystonia associated with baclofen overdose.

The dystonia requires no therapy but must be differentiated from seizure activity. Seizure activity is rarely (if ever) facial only. Spread to the hand is invariable and a useful clinical sign distinguishing twitch from seizure.

The last point regards the serum osmolality of 316 mmol/L and urine osmolality 183 mmol/L, leading to a diagnosis of diabetes insipidus.

In the patient reported, the blood alcohol of 0.16 g/dL is equal to 34 mmol/L blood alcohol and fully accounts for the serum hyperosmolality. The diagnosis of diabetes insipidus is difficult in the presence of alcohol. Alcohol does not effect tonicity but effects the measured osmolality.[2] Ethyl alcohol does not influence sodium concentration or water balance, effective osmolality or tonicity. Ethyl alcohol has direct effects on arginine vasopressin secretion further confusing the diagnosis. We would regard the patient as not hyperosmolar, thus we would not make the diagnosis of diabetes insipidus.

The patient described fits the pattern of Ehlers-Danlos syndrome type IV, a disorder of type II procollagen.[3] This genetic illness presents with major vessel rupture and a histological appearance similar to medial cystic necrosis.

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In reply

We thank Dr Bell for his careful critique which adds considerably to the case report "Complications of massive baclofen overdose".[1]

His recent patient recovered more rapidly than ours (24 hours vs 5 days) but was unlikely to have had a similar blood baclofen concentration (ours 20 mg/L). The case for similar severity of the two cases (and by implication for better management in Hobart) may have been stronger had this blood level been provided. Furthermore, it is worth noting that administration of benzodiazepines for relatively minor twitching, dystonias and myoclonic jerks is common for comatose patients in emergency departments and less so also in the intensive care unit. Dr Bell's point that this practice is unnecessary (both for his patient and for ours), of limited efficacy and is likely to delay recovery, is important. This is unlikely, however, to explain a 4 day period with fixed dilated pupils. His observation that a high admission blood ethanol negated the clinical diagnosis of diabetes insipidus is also very relevant. We support his conclusion and also note the absence of a cause for diabetes insipidus in this patient. There was no structural brain injury and the patient completely (although transiently) recovered.

Finally, his suggestion of Ehlers-Danlos syndrome type IV as a subclinical diagnosis in our case is outstanding and might well be correct. However, the possibility was not raised by the pathologist at autopsy and may be unlikely given the absence of characteristic skin thinness with subcutaneous vascular prominence which is part of this syndrome. It also remains unclear to us why an asymptomatic 47 year old should acutely

demise from arterial rupture at this particular time - during uncomplicated recovery from a massive sedative overdose.

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Intravenous infusions of Albumex®4 (human albumin 4%) and hypotension

CSL Bioplasma® has been made aware of an increase in reports of hypotensive episodes following use of colloid plasma expanders between March and August 2000. Of the reported cases in this interval, approximately 90% occurred following the sequential administration of a gelatin-based colloid (e.g. Gelofusine® or Haemaccel®) and Albumex®4. CSL has initiated a detailed investigation of these cases in co-operation with the reporting clinicians and has reviewed relevant available literature on hypotension related to use of gelatin-based colloids.

Increased activity of bradykinin and related substances are believed to contribute to many cases of colloid-induced hypotension. Bradykinin is usually degraded by endogenous angiotensin converting enzyme (ACE), however this is prevented in the presence of pharmacological inhibitors of ACE. As an endogenous inducer of bradykinin synthesis, prekallikrein activator (PKA), is present in blood-derived products, a potential for interactions between ACE inhibitors and the administration of blood-derived products such as Albumex®4 exists, and is presented as a precaution in our product information. Indeed, the potential for interactions between ACE inhibitors and colloidal albumin has been well documented in the literature over the past 20 years. CSL has improved the manufacturing process of all of our blood-derived products, including Albumex®4, so that PKA levels are now minimal and well below those prescribed by the relevant pharmacopoeias.

Of particular concern is the fact that gelatin-based plasma expanders have been shown to contain substances with an ACE inhibitor activity.[1] Consequently, there exists a potential for interaction between pharmaceutical ACE inhibitor therapy and the ACE inhibitory effects of gelatin-based plasma expanders such that the total ACE inhibitory activity may promote bradykinin accumulation and pose a risk of inducing hypotension. The clinical relevance of this potential is supported by recent case reports of hypotension following concomitant use of Gelofusine® and ACE inhibitors.[2,3]

A multicentre, retrospective analysis of 46,895 plasmapheresis procedures demonstrated a significantly higher incidence of hypotension and cardiovascular collapse when albumin and modified gelatin colloids were co-administered, in comparison with albumin administration alone.[4] This suggests a clinically relevant interaction between the ACE inhibitor effect of gelatin-based colloids and Albumex®4. Collectively, these data indicate that, whilst Albumex®4 is a safe plasma expander in cardiovascular surgery, there are concerns about the concomitant use of gelatin-based plasma expanders.

CSL is continuing to investigate these adverse events with the clinicians concerned and is seeking additional evidence that may help to dissect the relative contributions of ACE inhibitor therapy, gelatin-based plasma expanders and Albumex®4 to the observed episodes of hypotension. In the interim, we endorse the continued use of Albumex®4 in accordance with our product information. However, we caution against the concomitant use of Albumex®4 and gelatin-based plasma expanders, especially in those receiving ACE inhibitors. Where possible it would be prudent to withhold ACE inhibitors for at least 24 - 48 hr prior to infusion of either Albumex®4 or gelatin-based plasma expanders.

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