Acidosis, phosphofructokinase, and diabetic coma

Editor—In their recent article, Handy and Soni propose that ‘With regard to acidosis, the clinical literature is remarkable in its lack of conclusive evidence to support the perception that the acidosis itself is a detrimental state in need of direct correction’.

However, they have omitted the paper of Edge and colleagues which has shown that low blood pH is the immediate cause of coma. The glycolytic enzyme phosphofructokinase (PFK) is pH-dependent and its activity decreases with decreasing pH. Thus, the utilization of glucose in brain cells is impaired and, therefore, the clinical consequences of decreasing blood pH are drowsiness—stupor—coma—death in coma.

They also discuss diabetic ketoacidosis (DKA), which is only life threatening at its most severe stage, coma. There are reports with no deaths from coma in patients with DKA, where treatment included infusions of alkalizing solutions. Are there published reports with no deaths in similar comatose patients without infusions of alkalizing solutions?

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Editor—Dr Rosival highlights an extremely pertinent point in his response to our article; however, we disagree with the conclusions to which he has arrived from the quoted evidence. The study by Edge and colleagues highlights the association of acidosis with worse neurological effects during DKA in children. However, they provide no mechanism of causation and highlight in their discussion that the pathophysiological mechanism behind such neurological changes remains elusive. As stated in our article, association does not imply (or preclude) causation. It is of little surprise that patients with poorer clinical (neurological) presentation had worse metabolic derangement. Dr Rosival implies that the other studies showed improved outcomes using alkalinizing agents during management of DKA. The former study was a prospective non-interventional study not designed to elucidate the mechanisms of coma in DKA. The central tenet of the latter was a fluid resuscitation and management regime for patients with DKA which used a physiological approach, in which both bicarbonate and acetate were used as a part of anion replacement (rather than as alkalinizing therapy) and as a part of a complicated fluid management regime. It cannot be concluded from this that one part of a complicated regime is solely responsible for the overall outcome from that regime. Indeed this is not the conclusion of the original authors in either study.

Nevertheless, the role of acidosis in the inhibition of PFK is an interesting (and complex) one. Acidosis has a complex association with insulin resistance possibly through its effects on PFK or through alterations in cortisol metabolism. During insulin deficiency, cellular uptake of glucose is impaired, effectively depriving the cell of substrate for glycolysis. During this phase, the effects of cytosolic acidosis on PFK cannot be of significance as there is no or little glucose entering the pathway. On administration of insulin, however, it is possible that this cytosolic PFK inhibition may impair the ability to utilize glucose and thus delay cellular ATP production. The return of pyruvate as substrate for the Kreb’s cycle leads to increased Kreb’s metabolites which include malonyl-CoA. This is an important inhibitor of ketogenesis in the liver. Thus, if acidosis delays the return to aerobic metabolism in these circumstances, ketogenesis and ATP deficiency could theoretically persist. Such a mechanism has not, however, been mechanistically proven and (as we stated in our article), the results of experiments in cell lines, isolated organs, and differing species should be interpreted with caution when extrapolated to the clinical situation.

Returning to our original article, it is our view that mild to moderate acidoses are commonly encountered physiological and pathophysiological phenomena for which there is little evidence of direct causative detriment and which we tolerate relatively well. It is also our view that severe acidosis almost certainly does have detrimental effects: DKA is certainly such a state with severe metabolic derangement where the effects of acidosis could theoretically have direct detrimental effects. However, such effects remain to be proven.

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1 Handy JM, Soni N. Physiological effects of hyperchloreaemia and acidosis. Br J Anaesth 2008; 101: 141–50
Interlaminar approach for epiduroscopy in patients with failed back surgery syndrome

Editor—We read with interest the article by Avellanal and Diaz-Reganon.1 We acknowledge that they have demonstrated that the interlaminar approach for epiduroscopy is possible. However, we would argue with their conclusions that its diagnostic efficacy was clear, due to flaws in the design of the study and their high rate of complications.

There were small numbers involved in this study, a short duration of follow-up for a chronic condition, wide variations in pre-procedure management, no blinding, and no attempt to provide control subjects. There appears to be no attempt made to adhere to the core outcome measures as detailed in the IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) recommendations2 making acceptance of the findings more difficult. We have reservations over a technique which offers a 31.6% chance of no improvement and a 10% chance of making symptoms worse. The group who showed improvement (7/13) only had a one to two point improvement in their VAS (visual analogue scale). Is such a small decrease in VAS clinically significant? Possibly if the authors could have demonstrated a reduction in other core outcome measures such as physical and emotional functioning or drug use reduction. Unfortunately, they did not. In addition, they describe what we feel is an unacceptably high rate of complications. The authors describe 4/19 (21%) patients suffered dural puncture. This does not compare favourably in comparison with Igarashi and colleagues3 who had 1/58 (1.7%) patients suffer a dural puncture. A further 4/19 patients suffered transient neurological symptoms of headache or hypoacusia meaning that 8/19 (42%) patients had suffered a serious complication from the procedure. At no point in their study they mention other previously described complications which were felt not to be uncommon. This includes intravascular injection4 and visual disturbance.5

We have other reservations after reading the description of the technique. Using a solid 14 G Tuohy needle to introduce the epiduroscope raises two problems. First, how were they able to safely secure its position within the epidural space? Secondly, did they experience problems with shearing of the epiduroscope when they advanced and withdrew the catheter through the needle or when they rotated the Tuohy needle itself to help steer the epiduroscope? These are problems which one would not anticipate using the previously described route via a soft-tipped introducer placed through the sacral hiatus over a guidewire.

In conclusion, we felt that this approach for epiduroscopy, although physically possible, was not clinically appropriate on the grounds of weak evidence which shows low success rates and high complication rates. This paper is not going to alter the NICE guidelines6 which states that there is inadequate safety and efficacy evidence to support epiduroscopy other than for research and audit. This stance is further supported by the findings that targeted placement of epidural steroid is no better than an untargeted caudal epidural injection which is associated with a lower risk of complication.7

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Editor—We are grateful to Dr Fai and colleagues for their comments. The design of the study could possibly have been better set out and included more measures, but we used a system as in previous studies.7 8

In our study, 31.6% of the patients showed significant improvement which was maintained in all cases at 6 months, and we can now confirm that the improvement was maintained 1 yr later. These patients had previously had all the treatments available, including epidurolysis, without benefit. If we had not performed epiduroscopy, these patients (1/3) would have been required spinal cord stimulation. This means that one-third of our patients had relief from a serious pain problem and returned to their work and normal life without implantation of spinal cord stimulation systems. Moreover, in no case did the procedure make the patient worse. Therefore, we believe it to be clinically significant.

In relation to the rate of complications, we had 21% incidence of dural puncture. This is high in comparison with other studies.3 These are our initial results. We think that our patients cannot be compared with other series due to their high number of operations at lumbar level. On the other hand, only one patient suffered post-dural puncture headache. If you want to break adhesions down and reach the nerve roots in patients with strong adhesions, dural puncture during catheter advance must be considered as a side-effect. It can probably be diminished with practice. In fact, we have reduced the incidence of dural puncture to 10% in the last 20 procedures performed; in these cases, no patient suffered headache.