Paradoxical pain

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Relation of birth variables to death from cardiovascular disease

Edward D. J. Barker and colleagues' study puts a further nail in the coffin of those who doubt that the intrauterine environment influences later health—in this instance, death from cardiovascular disease. A theme running through the study is that there are no clear cut-ends to issues on this topic: that maternal nutrition is primarily responsible for reduced prenatal growth. Though there can be no doubting the importance of maternal malnutrition as a cause of reduced fetal growth in poor countries and the high perinatal mortality of the offspring, in the early part of this century, where Barker and colleagues' cohorts were born and brought up, there is no strong evidence of undernutrition now being responsible for restraining intrauterine growth in developed countries.

Maternal diet is only one of the many factors that can lead to fetal growth retardation. To begin to understand mechanisms that might link the environment of fetal life and infancy with later disease, we need to consider factors that are not well understood for example, Edwards et al. have recently proposed that links between the fetal environment, adult hypertension, and low birth weight could be mediated through dysfunction of the placental barrier to maternal cortisol.

Paradoxical pain

David Bowsher defines paradoxical pain as pain that is not relieved by morphine.^
1 It is more generally understood as pain that is made worse rather than better by increasing doses of morphine. It has been reliably reported with large doses of intrathoracic morphine or diamorphine and probably occurs occasionally with large daily doses of the same drug intravenously. Bowsher and his colleagues have made a good case for paradoxical pain being the result of a genetic inability to metabolise morphine to the potent morphine 6-glucuronide, leaving large quantities of morphine 3-glucuronide (a putative morphine antagonist or a non-specific cerebral stimulant, or both) unopposed. It is difficult, therefore, to understand why Bowsher has opted for an alternative description.

It is also disturbing that he has used “overwhelming pain” as a synonym for paradoxical pain. Overwhelming pain is a term used to emphasise a causally distinct result of chronic unrelieved severe cancer pain.
^
1 Paradoxical pain is a new and confusing term that has been defined in different ways. David Bowsher describes it as nociceptive pain that is not receptive (does he mean responsive?) to opioids. Yet in an earlier publication, in which the term was first coined, he and his colleagues used it to describe pain that was not relieved or was worsened by further administration of morphine or diamorphine (our italics). We have not seen any patients whose physical pain has been made worse by morphine or diamorphine, nor are we aware of any evidence that this could occur. More importantly, we fear that the suggestion that this may happen may deter some doctors from giving adequate doses of these drugs when they are properly indicated.

It is well recognised that opioid analgesics do not always relieve pain, and there are already several unsatisfactory ways in which such pain is described, including “opioid insensitive,” “opioid antiresponsive,” and “opioid resistant.” As we have written elsewhere, these terms have subtle differences in meaning, which are partly semantic but partly reflect different views. The introduction of yet another term will add confusion. We believe that what has been described as paradoxical pain is what we would refer to as “opioid poorly responsive” pain and that opioid responsiveness is a continuum that may be influenced by any of a large number of factors related to the patient and drug as well as the pain. The pharmacokinetics of morphine may provide at least part of the explanation, although there are too few data to justify the editorial’s subheading (morphine 3-glucuronide does not, by the way, bind to opiate receptors).

In 1967 Cicely Saunders described the concept of total pain, which encompasses the psychological, emotional, and spiritual turmoil of some patients with severe pain. Might this be what Bowsher refers to as overwhelming pain?

Robert Tyrnworz

Robert Tynwoz

Sir Michael Sobell House, University College, Oxford OX3 7LJ

Robert Tynwoz

EDITOR—David Bowsher’s editorial oversimplifies a complex and contentious issue. Paradoxical pain may well exist but is neither well documented nor common; it does not account for the majority of cases of uncontrolled pain, and we are not aware of any evidence that it was an important factor in the care of the patient in the recent highly publicised court case.

Hence the hypothesis that paradoxical pain is caused by abnormal metabolism of morphine is plausible but built on shaky foundations. The evidence in rats that morphine 3-glucuronide may antagonise the antinociceptive actions of morphine is unconfirmed and is hard to explain given that morphine 3-glucuronide has a much lower binding affinity for opioid receptors than either morphine or the active morphine metabolite, morphine 6-glucuronide. Furthermore, large interspecies variation exists not only in the metabolism of morphine but also in the distribution of opioid receptors.

Thus all data on this subject cannot, and should not, be extrapolated to humans and many questions remain.

Though recognition of this potential therapeutic problem is welcome, until the clinical importance of the morphine metabolites in humans is completely understood these rare cases of paradoxical pain will remain unexplained.

Carol J. Davis

EDITOR—The concept of paradoxical pain and its relation to morphine metabolites raises many questions. There are several conceptual errors inherent in this description. One of the most fundamental is that the pain syndromes as described should be on the basis of the epipeptide rather than the pain. This makes the assumption that so-called paradoxical pain is nociceptive pain, with the second assumption that all nociceptive pain

Robert Tynwoz

Sir Michael Sobell House, University College, Oxford OX3 7LJ

Robert Tynwoz

Department of Child Health, University College of Physicians and Surgeons, London WC1 2XX

D. P. Davids

J. M. T. Matthews


