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Melatonin: The Next Panacea?

Commentary on the article by Gitto et al. on page 756

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Neonatal sepsis is a frequent occurrence in the nursery. The morbidity associated with this condition is still significant despite the availability of antibiotics (1). This is due to factors other than the mere presence of an organism. In sepsis, liver mitochondria can increase rates of hydrogen peroxide and hydroxyl radical production *via* alterations in complex II activity (2). Cytokine release and resultant transcriptional activation of various genes can also result in increased reactive oxygen species (3). Some reports indicate that septic neonates have altered antioxidant status and several investigators have demonstrated increased oxidative stress in septic adults (2, 4). Based on this premise, Gitto and colleagues (5) evaluated the protective effects of melatonin therapy in neonates with sepsis by measuring a marker of oxidative stress.

In this small study involving only 20 newborns with sepsis, melatonin dissolved in 1:90 ethanol was administered orally to neonates within 24 -48 h diagnosis. Melatonin treated infants were less often classified as septic and demonstrated a reduction in markers of lipid peroxidation [malondialdehyde and 4-hydroxynonenal (4-HNE)]. This study provides encouraging evidence for the use of melatonin as an adjunct therapy in the treatment of neonatal sepsis. However, this study population is small and the criteria used for defining sepsis did not necessarily require that a blood culture be positive. Although we do not always identify the bacterial organisms responsible for neonatal sepsis, the lack of absolute confirmation of sepsis raises concerns about the nature of the illness in these patients. Would the infants have improved even if they were not given melatonin? Additionally, a change in serum malondiadldehyde and 4-HNE in the first four hours of life is difficult to reconcile with a change in clinical status 24 to 48 h later. We are not told whether this change persists or whether this difference was only transient. In either case, the association of decreased oxidative markers and improved clinical status is not necessarily causative.

As neonatologists, we are unfortunately quick to espouse therapies that later prove to be ineffective or harmful. As with most compounds, melatonin has multiple actions including its effect on the pineal gland and the sleep/wake cycle (6). The radical scavenging effects of melatonin have been proven *in vitro* and in animal models (7, 8) but the need for oral administration can be limiting in some instances where intestinal absorption is limited. This is particularly common in sick neonates. Furthermore, the vehicle, ethanol, can have both positive and negative effects. We have heard many reports on the antioxidant effects of moderate alcohol intake (9–11). This could suggest that the antioxidant effect of the melatonin preparation was not due entirely to melatonin itself although ethanol was used at very dilute concentrations. In contrast, ethanol ingestion can also cause oxidative stress (12) but this may be less relevant at the concentrations used in this study. This question is not answered because the controls did not receive the vehicle alone.

Despite these concerns, this study shows promise because multiple parameters of infection were altered in association with melatonin administration. Nonetheless, before heralding the next panacea, one must proceed with extreme caution. At the risk of stating the obvious and unoriginal, a large multicenter, randomized, controlled trial needs to be conducted to confirm whether this beneficial effect will survive more rigorous scrutiny.

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