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Opioid and benzodiazepine contributions to etomidate-associated adrenal insufficiency

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Dear Editor,
Both opioids and benzodiazepines independently and characteristically lower cortisol levels and may contribute to symptomatic adrenal insufficiency. The recent publications by Dr's den Brinker et al. [1] and Vinclair et al. [2] add to the ongoing debate regarding the importance of inhibited cortisol production in determining the most appropriate use of etomidate. However, as in other related studies, the authors did not consider possible contributions by concurrently administered medications to the lower cortisol levels in their patients.

The low cortisol levels associated with etomidate use have been associated with an increased death rate during prolonged use in ventilator-maintained subjects, and with symptomatic cortisol deficiency and occasional death following etomidate use in other patients. Etomidate-induced inhibition of cortisol production is now known to result from dose-related inhibition of 11-β-hydroxylase activity within the adrenal mitochondria, a phenomenon which has been extensively referenced by Lundy et al. [3] in his review.

Etomidate is a convenient anesthetic to use because of the speed with which it allows for intubation or pre-surgical induction, and because of the rapid recovery of patients with its discontinuation following surgical procedures. The on-going debate regarding its use includes uncertainties as to whether the low levels of cortisol associated with its use should be largely ignored, whether they justify marked curtailment of etomidate use, or whether they justify treatment with replacement cortisol in doses and for durations which have not been established.

Major contributions by concurrently administered opioids and benzodiazepines to etomidate-associated cortisol deficiency are strongly suggested by available data. Either or both of these medications have been administered to the patients described in most adequately detailed case reports of etomidate-associated adrenal insufficiency. Patients reported by den Brinker et al. [1] commonly received opioid agonists or midazolam, and their mechanically ventilated children were sedated with benzodiazepines and/or morphine. Similarly, the patients reported by Vinclair et al. [2] typically received midazolam or opioids. Patients reported in the studies cited by Lundy et al. [3] present a similar pattern, while none of these reports acknowledge a possible contribution to etomidate-associated cortisol deficiency by these concurrently administered medications.

Opioids administered to opioid-naïve subjects rapidly and profoundly inhibit both stress-related cortisol production and cortisol response to cosyntrophin stimulation [4], while chronic opioid consumers occasionally manifest adrenal crises [5], phenomena apparently induced by inhibition of the HPA axis at multiple sites.

Benzodiazepines, similarly, quickly induce diminished cortisol formation by inhibiting activity at multiple central and peripheral sites in the HPA axis, including that of adrenal microsomal 17- and 21-hydroxylase activity as well as 11-β-hydroxylase activity in adrenal mitochondria [6], thereby augmenting the inhibition at this site induced by etomidate. Adrenal inhibition during combined fentanyl-diazepam anesthesia has been widely documented.

These observations strongly indicate a need for studies examining the inhibition of adrenal function induced by contributions of etomidate or other rapid acting anesthetic agents in combination with opioids, benzodiazepines, and other analgesic and sedative medications, in order to identify the safest, most effective, and most convenient combinations of these drugs.

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