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## After Transdermal Fentanyl: Acute Toxic Delirium or Central Anticholinergic Syndrome?

*To the Editor:*—Kuzma *et al.*<sup>1</sup> describe a 14-yr-old boy in a "confusional state" after an increase in the dosage of transdermal fentanyl. Their differential diagnoses comprised neurological, psychiatric, and systemic diseases, as well as endocrinological, metabolic, respiratory, and infectious disorders. Assuming that the adjective "toxic" denotes that the real cause of the observed condition is unknown, no definite conclusion was reached.

The symptom "extreme agitation" described by the authors, in association with fentanyl medication, is compatible, besides others, with the diagnosis "central anticholinergic syndrome" (CAS), as described by Longo<sup>2</sup> after atropine, by Holzgrafe *et al.*<sup>3</sup> after scopolamine and anesthesia, by Duvoisin and Katz<sup>4</sup> after scopolamine or trihexiphenidyl, and by Granacher and Baldessarini<sup>5</sup> after multiple neuropsychiatric medications. The syndrome has been observed not only with known anticholinergics, but also with anesthetics, hypnotics, sedatives, and opioids.<sup>6</sup> Also, other drugs passing the blood brain barrier (e.g., mefloquine,<sup>7</sup> an antimalarial drug) can cause the syndrome. Because the clinical picture of the syndrome is extremely variable—symptoms ranging from deep coma to extreme agitation—a systematic description is difficult. Unfortunately, no specific laboratory tests are given and the diagnosis can only be confirmed "ex juvantibus." Treatment with physostigmine, a cholinesterase inhibitor passing the blood brain barrier, in a dosage of 0.03–0.04 mg/kg, has proven to resolve the symptoms promptly. Serious side effects are not reported if the contraindications are obeyed.<sup>3,6</sup>

The common pathophysiologic basis for the extremely variable symptoms encountered with CAS is an impairment of the central cholinergic transmission.<sup>5</sup> With respect to some opioid analgesics, there is experimental evidence that these substances reduce the release of acetylcholine in the cerebral cortex.<sup>8</sup> For fentanyl, dose dependent binding to muscarinic receptors in the brain has been shown.<sup>9</sup>

After an increased dosage of fentanyl, the symptoms in the patient described<sup>1</sup> support the tentative diagnosis CAS. It is conceivable that a single injection of physostigmine would have resolved the condition. By doing so, nothing is lost if CAS is not the underlying cause and the condition does not change; in the presence of CAS, the patient is saved from being transferred to the intensive care unit and from costly and time-consuming diagnostic procedures. Central anticho-

linergic syndrome has been called a "forgotten diagnosis."<sup>\*\*</sup> It might be helpful, in a case as described, to include this syndrome in the differential diagnoses.

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