Venlafaxine: Troubling toxicity in overdose

Venlafaxine (Effexor), a serotonin and norepinephrine reuptake inhibitor, entered the Canadian market in 1994. As with any new medication, experience with overdose was extremely limited when venlafaxine was introduced. Although only 12 suicide attempts had been recorded at launch, because there were no deaths and only one seizure, it was hoped that it would be safer in overdose than other antidepressants.[1] Since this initial optimism, however, the toxic consequences of venlafaxine overdose quickly became evident. By 1996, numerous overdose cases from poison centres reported tachycardia, hypotension, seizures, coma, serotonin syndrome, and death.[2-8]

The relative toxicity of venlafaxine in overdose compared with other antidepressants was first highlighted in an analysis of United Kingdom mortality data published in 2002.[9] In overdose from a single antidepressant, venlafaxine was found to have a fatal toxicity index of 13.2 deaths/million prescriptions (95% CI 9.2–18.5), which was comparable to clomipramine (12.5 deaths/million prescriptions; 95% CI 9.4–16.3). Among serotonergic antidepressants, the maximum fatal toxicity index was 3.0 deaths/million prescriptions (95% CI 0.3–10.9) for fluvoxamine. Venlafaxine has been found to result in a greater likelihood of ICU admissions than selective serotonin reuptake inhibitors (SSRIs)[10] and appears more likely than SSRIs to cause serotonin syndrome, seizures, and QRS prolongation to ≥ 100 msec.[10] Venlafaxine has similar ECG changes to those observed with tricyclic antidepressant (TCA) overdosage, exhibiting QRS widening and QTc interval prolongation, possibly due to sodium-channel blockade.[11] The odds ratio of venlafaxine causing seizures compared with TCAs is estimated to be 4.4 (95% CI 1.4–13.8).[10]

The Poison Control Centre at BC's Drug and Poison Information Centre (DPIC) has had over a decade of involvement with venlafaxine overdose management. DPIC experience is consistent with published literature, with numerous cases of both adults and teens exhibiting tachycardia, hypotension, serotonin syndrome, and precipitous seizures following venlafaxine overdose as well as cases of QTc prolongation and QRS widening. In the interest of patient safety and pharmacovigilance, DPIC continues to gather data on venlafaxine overdose in BC, to advise on case management, and to follow up for outcomes. Accumulating evidence of fatalities has recently prompted Wyeth in the United States to revise its Effexor prescribing information.[12] They advise that the risk of fatal outcome following venlafaxine overdose may be increased compared with SSRI antidepressants but is lower than that following TCA overdose.

Venlafaxine has been found to result in a greater likelihood of ICU admissions than SSRIs.

To increase awareness of the serious problems with venlafaxine overdose, DPIC has recently highlighted venlafaxine toxicity in its *Toxic Update Newsletter.* This is being distributed to emergency departments and interested physicians throughout BC. To obtain a copy or to be placed on the newsletter distribution list, e-mail your request to info@dpic.ca.

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