Prolonged delirium without anticholinergic signs following amitriptyline overdose

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In a case of acute intoxication with a tricyclic antidepressant (amitriptyline) delirium was prolonged without there being prominent peripheral anticholinergic or electrocardiographic signs. Administration of physostigmine, repeated when necessary, reversed the delirium.

Dans un cas d'intoxication aiguë à un antidépresseur tricyclique (amitriptyline) le délire s'est prolongé en l'absence de signes manifestes d'un effet anticholinergique périphérique ou d'une modification de l'électrocardiogramme. L'administration de physostigmine, répétée au besoin, a fait rétrocéder le délire.

When an adequate history is unavailable the diagnosis of tricyclic antidepressant (TCA) intoxication is based upon the clinical features, the laboratory findings and the response to physostigmine administration.

Delirium is a prominent feature of TCA intoxication and is commonly accompanied by anticholinergic effects, such as pyrexia, mydriasis, flushing, dryness of the skin and mucous membranes, urinary retention and depressed bowel activity.[1,2] Most patients have sinus tachycardia and electrocardiographic abnormalities that include nonspecific ST-segment and T-wave changes, a widened QRS complex, and prolonged PR and QT intervals.[1,3,4] Conduction blocks are also frequent.[4]

We report the following case of prolonged TCA-induced delirium with minimal anticholinergic signs and no electrocardiographic signs.

Case report

A 66-year-old Caucasian woman was brought to the emergency room because of abnormal behaviour. She had last been seen in her usual state of good health 2 days earlier. She was fearful, irritable and startled by minor stimuli. There was constant fidgeting and coarse tremulousness of the arms. Her speech was rambling and unintelligible. She ignored commands and could not sustain meaningful contact with others. She seemed to be experiencing visual hallucinations and reached for nonexistent objects. The findings in a general physical examination were unremarkable except for distension of the bladder; there were no other anticholinergic signs. The pulse rate was 80 to 96 beats/min. Our clinical impression was that she had acute delirium of a toxic, metabolic or infectious origin.

Laboratory studies, including measurement of the blood electrolyte, urea nitrogen and blood glucose levels, a complete blood count, determination of arterial blood gas values and urinalysis, gave normal results. An electrocardiogram was also normal, with no cardiac arrhythmias detected during continuous monitoring. Chest and skull x-ray films and the results of analysis of the cerebrospinal fluid were normal.

Thirty hours later there was no change in the patient's status. However, a history of depression that had recently been treated with amitriptyline and methotrimeprazine (a phenothiazine derivative) was obtained from her estranged husband. Physostigmine, 2 mg, was then given intravenously, and within 3 minutes all evidence of delirium ceased. Apart from mild diaphoresis no cholinergic effects or changes in vital signs were noted. The patient admitted to having ingested 50 amitriptyline tablets (10 mg each) and 10 methotrimeprazine tablets (25 mg each) 66 hours before the administration of physostigmine. Three hours later delirium recurred and was again reversed with physostigmine, 2 mg. Four more such doses of physostigmine were required to reverse delirious states that recurred at variable intervals. Following the sixth and final dose of physostigmine, 120 hours (5 days) after the excessive ingestion of drugs, the patient's mental status remained normal. No other drugs were administered.

Samples of the patient's serum obtained after the first dose of physostigmine had been given and 24 hours later (66 and 90 hours after the excessive ingestion of drugs) were analysed. Gas chromatography–mass spectroscopy revealed amitriptyline, 183 ng/ml, and nortriptyline, 390 ng/ml, in the first sample and amitriptyline, 124 ng/ml, and nortriptyline, 450 ng/ml, in the second. Extensive toxicologic analysis failed to reveal phenothiazines or other drugs.

Discussion

Previous descriptions of adults with antidepressant-induced delirium that could be reversed by physostigmine have noted obvious peripheral anticholinergic signs, sinus tachycardia or both.[2,5-7] When caused by an acute overdose, the delirium lasted less than 8 hours.[5,6] In our patient there were no obvious anticholinergic signs, and the delirium lasted 5 days.

Although the serum amitriptyline level in this patient declined over a 24-hour period, the drug's active metabolite, nortriptyline, accumulated, so that the total TCA levels were the same (573 and 574 ng/ml). The optimal therapeutic serum level of amitriptyline (the total serum concentrations of amitriptyline and nortriptyline) is 150 to 250 ng/ml.[8] Total concentrations greater than 450 ng/ml have frequently been associated with delirium.[2] Prolonged

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elevations of total TCA plasma levels have been documented following overdoses[9] and in our patient may be explained by an age-related reduction in the clearance of amitriptyline.[10] This may explain her prolonged delirium and the transient benefit of physostigmine administration.

Our case demonstrates that acute TCA intoxication may produce a prolonged delirium, without prominent peripheral anticholinergic and electrocardiographic signs, that may be reversed by repeated doses of physostigmine.

References

1. NOBLE J, MATTHEW H: Acute poisoning by tricyclic antidepressants: clinical features and management of 100 patients. *Clin Toxicol* 1969; 2: 403–421

2. PRESKORN SH, SIMPSON S: Tricyclic-antidepressant-induced delirium and plasma drug concentration. *Am J Psychiatry* 1982; 139: 822–823

3. BAILEY DN, VAN DYKE C, LANGOU RA, JATLOW PI: Tricyclic antidepressants: plasma levels and clinical findings in overdose. *Am J Psychiatry* 1978; 135: 1325–1328

4. SPIKER DG, WEISS AN, CHANG SS, RUWITCH JF JR, BIGGS JT: Tricyclic antidepressant overdose: clinical presentation and plasma levels. *Clin Pharmacol Ther* 1975; 18: 539–546

5. HEISER JF, WILBERT DE: Reversal of delirium induced by tricyclic antidepressant drugs with physostigmine. *Am J Psychiatry* 1974; 131: 1275–1277

6. JANSON PA, WATT JB, HERMOS JA: Doxepin overdose. Success with physostigmine and failure with neostigmine in reversing toxicity. *JAMA* 1977; 237: 2632–2633

7. SCHUSTER P, GABRIEL E, KÜFFERLE B, KAROBATH M: Reversal by physostigmine of clozapine-induced delirium. *Lancet* 1976; 1: 37–38

8. ZIEGLER VE, CO BT, TAYLOR JR, CLAYTON PJ, BIGGS JT: Amitriptyline plasma levels and therapeutic response. *Clin Pharmacol Ther* 1976; 19: 795–801

9. SPIKER DG, BIGGS JT: Tricyclic antidepressants. Prolonged plasma levels after overdose. *JAMA* 1976; 236: 1711–1712

10. HENRY JF, ALTAMURA C, GOMENI R, HERVY MP, FORETTE F, MORSELLI PL: Pharmacokinetics of amitriptyline in the elderly. *Int J Clin Pharmacol Ther Toxicol* 1981; 19: 1–5