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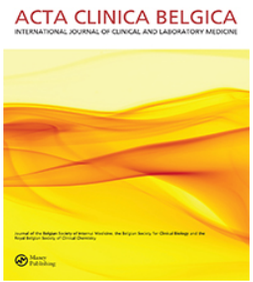

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FATAL OVERDOSE WITH TRAZODONE : CASE REPORT AND LITERATURE REVIEW

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Key words : arrhythmia, death, trazodone

ABSTRACT

A fatal case of suicide with trazodone alone in a 40-year-old patient is reported. Life-threatening arrhythmias, such as torsades de pointes and complete AV block, are recorded. Blood collected at admission contained a trazodone toxic concentration of 25.4 µg/mL. The patient developed multiple organ failure and died less than 24 hours after his admission to the emergency department. The authors discuss the effects of overdose of trazodone, a well-known safe antidepressant drug.

INTRODUCTION

Trazodone has an efficacy similar to tricyclic antidepressants (1-2). Side-effects (sleepiness, nausea, fatigue, dizziness, headache, insomnia) are uncommon; this drug is said to have a low level of toxicity, even in case of overdose and has a very favourable efficacy/side effects ratio, comparing to other antidepressants (1-2). We, however, report one fatal case due to acute overdose. Cardiac arrhythmias, such as torsades de pointes and a complete AV block, have been recorded and tend to prove direct myocardial toxicity of this drug. To our knowledge, only one similar case of death due to trazodone overdose alone has been published in the medical literature (3).

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CASE REPORT

A 40 years-old man is admitted to the emergency room. His medical history includes severe depression, treated with trazodone (Trazolan ® 100 mg/day, Continental Pharma) and fluvoxamine (Floxyfral ® 100 mg/day, Solvay). On the day of his admission, at sunrise, his wife found him lying unconscious on his bed. She felt weak pulses and a shallow breath. The reanimation ambulance came quickly to the patient's house. At this time, BP was unobtainable and his pulse was at 30-40 bpm. The patient was assigned a score of 3 on the Glasgow coma scale and required intubation for ventilatory support. At this time, asystole was recorded. CPR was started and 1 mg of adrenaline was IV administered.

The patient was immediately transferred to our coronary care unit. Physical examination revealed a normally coloured patient. The temperature was 36°8 C, the BP 150/70 mmHg and a regular pulse of 120 bpm. Cardiac examination revealed normal heart sounds, no murmurs, gallops, rubs or clicks. The remainder of physical examination showed a dry mouth, bilateral dilated pupils and distended bladder, without enlarged prostate.

Initial therapy, including colloids, bicarbonate, insulin, extra potassium, was given intravenously, without initial digestive decontamination, due to unawareness of acute intoxication. Initial laboratory studies disclosed blood glucose, 454 mg/dL (Reference range : 60-90 mg/dl); sodium, 140 mmol/L (Reference range : 136-145 mmol/L); potassium, 3 mmol/L (Reference range : 3.5-5 mmol/L); and lactate, 14.2 mmol/L (Reference range : 0.5-2.2 mmol/L). A first urinalysis for barbiturates, tricyclic agents, and benzodiazepines yielded negative. The 12-lead electrocardiogram showed sinus rhythm and nonspecific ST-T wave abnormalities; the QT interval was recorded at 410 msec. Echocardiography was normal. Life-threatening arrhythmias were thereafter observed : recurrent torsades de pointes (fig.1) recorded after sixth hours, followed by ventricular fibrillation on two occasions,

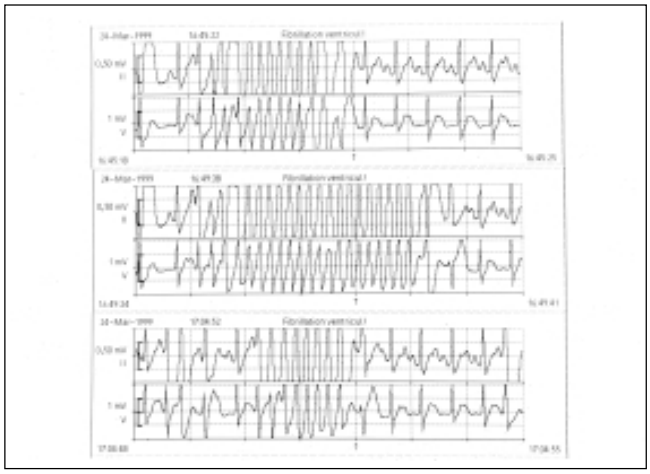

Figure 1 : Three ECG strips showing the onset of torsades de pointes. Note the prolonged QT interval and the long-short cycles preceding the onset of the arrhythmias.

and a complete AV block, with a QRS complex duration of 120 msec and QTc interval prolongation at 520 msec recorded after eighth hours (fig.2). Therapy followed thereafter included intravenous magnesium, correction of hypokalaemia and insertion of a temporary pacemaker. Intravenous sodium lactate solution was not infused, since the exact diagnosis of the overdose was still unknown at that time. Unfortunately, the patient underwent several complications : temperature > 39°C, shock, multiple organ failure with anuria and renal failure, hypoxic hepatitis and disseminated intravascular coagulation. A complete toxicological screening allowed the exclusion of toxic ingestion such as alcohol, methanol, lithium, tricyclic agents, barbiturates, cocaine or benzodiazepines. On admission, the

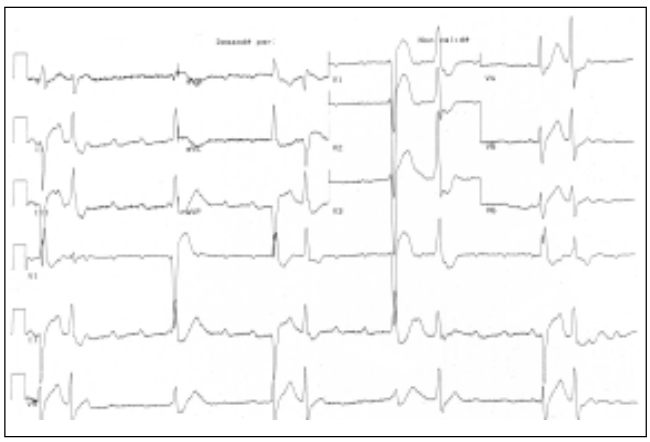

Figure 2 : 12-lead ECG showing complete AV block, ventricular extrasystole, intraventricular conduction disturbances, and a prolonged QT interval at 520 msec.

trazodone concentration however reached a toxic level at 25.4 µg/mL (therapeutic concentrations : 1-1.5 µg/mL). After 30 hours, neurological examination showed an unresponsive patient, BP at 50/30 mmHg under inotropes (dopamine 20 µg/kg/min and norepinephrine 20 µg/kg/min). Evoked potentials and electroencephalogram were flat. Progressive hemodynamic deterioration ensued, and the patient died soon afterwards.

DISCUSSION

Trazodone, a triazolopyridine derivative, is a second-generation antidepressant, with a unique chemical structure and a pharmacological profile slightly different from other tricyclic agents. It is also noticeable for its weak anticholinergic properties. This drug was showed to be efficient and safe even in cases of voluntary or accidental overdose (1-2, 4).

Cardiovascular toxicity has been known for a long time with the tricyclic antidepressant agents (4-6). It includes orthostatic hypotension, conduction disturbances and life-threatening arrhythmias (torsades de pointes and ventricular fibrillation) due to the pro-arrhythmic effects of these drugs. A 12-lead electrocardiogram has to be recorded before any tricyclic prescription. A prolonged QT interval should advise against prolonging the intake of these drugs. Association with other medications that prolong QT interval (antiarrhythmic drugs, antidepressants, antihistamines, ...), in any case, should be forbidden.

Trazodone has been reported to have less severe cardiotoxic effect. It was recommended in cases of arterial hypotension, cardiac failure and after myocardial infarction. Reported cases of severe trazodone overdose, taken without any other drug in combination, are shown in table 1 (3, 7-11). Hypotension, coma, seizures due to hyponatremia and cardio-respiratory arrest were the most common complications. Augenstein et al. described the other case of death after a significant overdose (4.5 g) of trazodone (3). Several other fatal cases are reported but, in each one, trazodone was taken together with other drugs (7-8, 12). Root described the case of a surviving patient with a trazodone concentration of 25.7 µg/mL, following ingestion of an estimated dose of more than 4 grams (7). This toxic concentration was similar to that in our case with a fatal consequence.

Electrocardiographic changes included a transient first-degree AV block in one case, T wave inversion in

one other case, bradycardia and QT interval prolongation, leading to the life-threatening arrhythmias (torsades de pointes and ventricular fibrillation) in the remaining 3 cases (Table 1) (3, 8, 11). These two arrhythmias were recorded in our patient. The strips of torsades de pointes did not have the typical morphology but the presence of bradycardia with prolonged QT interval was sufficient to confirm the diagnosis.

Fluvoxamine, another medication given to our patient, but without any documented overdose, is a selective inhibitor of the reuptake of presynaptic serotonin. Trazodone, although not selective, has a similar effect. Cases of malignant serotonin syndrome have been published; symptoms include confusion, agitation, poor concentration, myoclonus, rigidity, hyperreflexia, fever and, rarely, coma, rhabdomyolysis or death (13). These symptoms are to be searched for with all tricyclic antidepressant agents. In our particular case, fever and fatal evolution towards multiple organ failure could suggest the association of major overdose and serotonin syndrome. This multiple organ failure was probably not only related to a prolonged circulatory insufficiency, due to the arrhythmias.

To conclude, when taken alone in overdose, trazodone appears to have limited cardiac toxicity. Nevertheless, in each case, we formally advise urgent therapy and intensive care similar to that applied with other tricyclic antidepressant overdoses.

RÉSUMÉ

Les auteurs rapportent un cas fatal d'autolyse par la trazodone seule chez un patient de 40 ans, dépressif de longue date. Des complications d'arythmies létales, telles des torsades de pointes et un bloc auriculo-ventriculaire complet sont objectivés. Le taux sérique de trazodone de 25.4 µg/mL est prélevé à l'admission. Le patient décède de défaillance multi-organique, moins de 24 heures après son admission en urgence. Les auteurs revoient les effets d'une overdose à la trazodone, un antidépresseur réputé peu toxique.

TABLE 1 : Characteristic data of reported cases involving trazodone overdose, taken without any other drug in combination.

Patient [reference]	Age/sex	Dose	[T] blood	Complications	ECG	Status
1. [7]	49y / F	4-8 g	25.7 µg/mL	hypotension	–	alive
2. [8]	40y / M	2.2 g	–	hypotension, respiratory arrest	–	alive
3. [8]	50y / F	3 g	–	respiratory arrest, seizures	–	alive
4. [8]	24y / M	3.5 g	–	priapism	–	alive
5. [3]	30y/ F	4.5 g	–	coma, renal failure, cardiac arrest	bradycardia QT ↑, TdP	dead
6. [9]	72y / F	0.35g	–	Hyponatremia (118 mmol/L), seizures	–	alive
7. [10]	60y / F	1.2 g	–	hyponatremia (106 mmol/L), seizures	–	alive
8. [11]	29y / F	3 g	–	Coma	bradycardia, QT↑	alive
9. [*]	40y/ M	?	25.4 µg/mL	coma, fever, shock, multiple organ failure, cardiac arrest	bradycardia, QT ↑, TdP, AV block	dead

Dose = ingested dose of trazodone, [T] blood = blood concentration of trazodone, ECG = electrocardiogram, QT ≠ = QT interval prolongation, TdP = Torsades de pointes, [*] = our case report.

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