

# 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.<sup>1,2</sup> 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.<sup>1,3,4</sup> Conduction blocks are also frequent.<sup>4</sup>

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

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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 non-existent 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.<sup>2,5-7</sup> When caused by an acute overdose, the delirium lasted less than 8 hours.<sup>5,6</sup> 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.<sup>8</sup> Total concentrations greater than 450 ng/ml have frequently been associated with delirium.<sup>2</sup> Prolonged

elevations of total TCA plasma levels have been documented following overdoses<sup>9</sup> and in our patient may be explained by an age-related reduction in the clearance of amitriptyline.<sup>10</sup> 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

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## Intermediate Prescribing Information

# Trasicor®

## Slow-Trasicor® tablets

(oxprenolol hydrochloride)  
Antihypertensive Agent

### Actions

TRASICOR (oxprenolol hydrochloride) is a non-cardio-selective beta-adrenergic-receptor-blocking agent which possesses partial agonist activity. It is used in the treatment of hypertension.

### Indications

*Mild or moderate hypertension.* Usually used in combination with other drugs, particularly thiazide diuretics, however, may be tried alone as an initial agent in those patients whose treatment should be started with a beta-blocker rather than a diuretic. Oxprenolol hydrochloride therapy should start using TRASICOR (regular formulation), and once the maintenance dosage has been established, SLOW-TRASICOR may be substituted (see *Dosage & Administration*).

The combination of TRASICOR with a diuretic and/or peripheral vasodilator has been found to be compatible and generally more effective than TRASICOR alone. Experience with other antihypertensive agents has not shown evidence of incompatibility.

Not recommended for the emergency treatment of hypertensive crises.

### Contraindications

Bronchospasm (including bronchial asthma), allergic rhinitis during the pollen season, sinus bradycardia and greater than first degree A-V block, right ventricular failure secondary to pulmonary hypertension, congestive heart failure, cardiogenic shock, anesthesia with agents that produce myocardial depression, e.g. ether.

### Warnings

#### a) Cardiac Failure

Special caution should be exercised when administering TRASICOR to patients with a history of heart failure since inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure.

At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. TRASICOR does not abolish the inotropic action of digitalis on the heart muscle, however, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of TRASICOR when the two drugs are used concomitantly. The effects of beta-blockers and digitalis are additive in depressing A-V conduction. If cardiac failure continues, despite adequate digitalization and diuretic therapy, TRASICOR therapy should be immediately withdrawn.

#### b) Abrupt Cessation of Therapy with TRASICOR

Warn patients against abrupt discontinuation. There have been reports of severe exacerbation of angina and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. When discontinuation of TRASICOR is planned in patients with angina, TRASICOR should be substituted for SLOW-TRASICOR and then the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, TRASICOR therapy should be discontinued in stepwise manner under closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with TRASICOR be reinstated promptly, at least temporarily.

c) Various skin rashes and conjunctival xerosis have been reported. A severe syndrome (oculo-mucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasisiform rashes, otitis, and sclerosing keratitis has occurred with the chronic use of one beta-adrenergic-blocking agent, practolol but has not been observed with TRASICOR or any other such agent. Physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

d) Severe sinus bradycardia may occur; in such cases, dosage should be reduced and the use of atropine and isoproterenol considered.

e) TRASICOR may mask the clinical signs of continuing hyperthyroidism or its complications; therefore, abrupt withdrawal of TRASICOR may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm. TRASICOR does not alter thyroid function tests.

### Precautions

a) In patients prone to non-allergic bronchospasm (e.g. chronic bronchitis, emphysema), TRASICOR should be administered with caution since it may block the bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta<sub>2</sub> receptors.

b) Administer with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia. Dosage of antidiabetic drugs may need to be adjusted.

c) Adjust dosage appropriately when used in conjunction with other anti-hypertensive agents.

d) Closely monitor patients also receiving catecholamine-depleting drugs, such as reserpine or guanethidine. The added beta-adrenergic-blocking action of this drug may produce an excessive reduction of sympathetic activity.

e) Appropriate laboratory tests should be performed at regular intervals during long-term treatment.

f) TRASICOR should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy (see *Warnings*).

Available evidence suggests all clinical and physiological effects of beta-blockade are no longer present 48 hours after cessation of medication.

In emergency surgery, effects of TRASICOR may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levaterterenol.

g) *Usage in Pregnancy and Nursing Mothers:* Not recommended in pregnancy or lactation. Oxprenolol hydrochloride passes into the breast milk.

h) *Usage in children:* Although experience is limited, TRASICOR is not recommended for pediatric use.

i) After the active substance has diffused out of the insoluble core of the SLOW-TRASICOR tablet, the empty matrix excreted in a softened form and may be found in the feces.

### Adverse reactions

#### Cardiovascular:

Congestive heart failure (see *Warnings*); pulmonary edema, cardiac enlargement; secondary effects of decreased cardiac output which include: syncope, vertigo, lightheadedness and postural hypotension; severe bradycardia; lengthening of PR interval; Second and third degree A-V block; sinus arrest; palpitations; chest pains; cold extremities; Raynaud's phenomenon; claudication; hot flushes.

*Respiratory:* Shortness of breath, wheezing, bronchospasm status asthmaticus.

*Central Nervous System:* Headache, dizziness, anxiety, mental depression, nervousness, irritability, hallucinations, sleep disturbances, including nightmares and insomnia. Tinnitus, weakness, sedation, vivid dreams, vertigo, paresthesia and slurred speech.

*Gastrointestinal:* Diarrhea, constipation, flatulence, heartburn, anorexia, nausea and vomiting, abdominal pain, dryness of mouth.

*Allergic/Dermatological:* (see *Warnings*)

Rash (psoriasisiform and exanthematic); dry skin, pruritus; sweating.

*Ophthalmological:* Conjunctivitis, dry eyes, itching eyes, blurred vision.

*Miscellaneous:* Emptied, decreased libido, nasal stuffiness, weight gain.

*Clinical Laboratory:* Elevated transaminases, BUN, alkaline phosphatase and bilirubin have occurred in some patients. Thrombocytopenia and leucopenia, and hypoglycemia have also been reported rarely.

### Symptoms and Treatment of Overdosage

*Symptoms:* bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

*Treatment:* Discontinue TRASICOR and observe patient closely. If required, the following therapeutic measures are suggested:

1. Bradycardia: Atropine or another anticholinergic drug.
2. Heart block (second degree or total): isoproterenol or transvenous cardiac pacemaker.
3. Congestive heart failure: Conventional therapy.
4. Hypotension (depending on associated factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.
5. Bronchospasm: Aminophylline and/or isoproterenol; or a beta<sub>2</sub>-adrenergic agonist.
6. Hypoglycemia: Intravenous glucose.

Large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of TRASICOR. However, the complications of excess isoproterenol should not be overlooked.

### Dosage and Administration

*Initial Dosage:* Initiate with TRASICOR (regular formulation), 20 mg t.i.d., followed by upward titration of the dose on a t.i.d. basis, with increases of 60 mg per day at one- to two-week intervals until adequate control of blood pressure is obtained.

*Maintenance Dosage:* Once the optimal dose has been established, the total daily dose of TRASICOR (regular formulation) may be given on a b.i.d. schedule, although no comparison studies between the t.i.d. and b.i.d. regimen have been carried out. Alternatively, an equivalent single daily dose of SLOW-TRASICOR may be substituted, and should be taken in the morning. SLOW-TRASICOR tablets should be swallowed whole.

*Usual Daily Dose:* 120-320 mg, should not exceed 480 mg.

### Availability

TRASICOR 20 mg tablet: white, round, slightly biconvex with bevelled edges, film coated. Imprint on one side: CIBA. Imprint on the other side: SR. Bottles of 100 tablets.

TRASICOR 40 mg tablet: white, round, slightly biconvex with bevelled edges, film coated. Imprint on one side: CIBA. Imprint on the other side: AI, separated by a score. Bottles of 100 and 500 tablets.

TRASICOR 80 mg tablet: light yellow, round, slightly biconvex with bevelled edges, film coated. Imprint on one side: CIBA. Imprint on the other side: CG, separated by a score. Bottles of 100 and 500 tablets.

SLOW-TRASICOR 80 mg tablet: light red, round, slightly biconvex, film coated. Imprint on one side: CIBA. Imprint on the other side: BEB.

SLOW-TRASICOR 160 mg tablet: white, round, slightly biconvex, film coated. Imprint on one side: CIBA. Imprint on the other side: BNB. Bottles of 50 tablets.

Product Monograph supplied on request.