CASE REPORT

Dextropropoxyphene and the cardiovascular system: About two cases of acute poisoning with cardiac conduction abnormalities

Frédérik Staikowsky, MD, PhD
Sébastien Candella, MD
Maurice Raphael, MD

INTRODUCTION

Dextropropoxyphene (DP) is a mildly analgesic synthetic opiate structurally related to methadone. Peak plasma concentrations are reached 2.0 to 2.5 hours after oral administration. N-demethylation is the major biotransformation pathway of DP to norpropoxyphene (NP). The manifestations of acute overdose with DP are similar to those of narcotic overdose. DP poisoning may also result in cardiac failure and arrhythmias. These cardiac side effects are the result of a local anesthetic effect.

The effectiveness of naloxone to reverse all opiate features in DP poisoning is well established. However, data from animal and human reports suggest that naloxone fails to reverse DP cardiotoxicity. Positive inotropic drugs are usually used to treat cardiac failure. In uncommon cases, lidocaine and sodium bicarbonate have been successfully used in the management of cardiac conduction abnormalities.

Acute intoxication by ingestion of DP is considered to be easily treatable with low mortality rate at hospital. However, legal medicine institutes in the United States, the United Kingdom, and the Nordic countries have reported a pronounced proportion of prehospital deaths.[1-3] The majority of these deaths are attributed to cardiovascular complications and opioid effects.[3] Restriction of availability and even total withdrawal of DP from the market are currently being debated in some countries. Observation of the following two cases has led to discussion of the links between the cardiovascular system and DP.

CASE REPORTS

Case 1

A 29-year-old man was admitted for acute self-ingestion of flunitrazepam, bromazepam, paracetamol, and DP (1.3 g); the patient was a former heroin addict who took benzodiazepine and DP (650 to 1,300 mg per day) as a substitute. On admission, he was conscious but restless. He suddenly presented a generalized convulsive crisis and, after resolution, the neurological examination was normal apart from altered consciousness and constricted pupils. Seizures were recurrent. The blood pressure was low (70/40 mmHg) and the heart rate 55 beats per min. The patient was also cyanosed and bradypneic, with the following arterial blood gases in ambient air: pH 7.09, HCO_3^- 20 mmol per L, $PaCO_2$ 9.80 kPa, PaO_2 6.10 kPa, SaO_2 65 percent (normal ranges: pH 7.38 to 7.42, HCO_3^- 22 to 25 mmol per L, $PaCO_2$ 4.9 to 5.6 kPa, PaO_2 12 to 14 kPa, SaO_2 > 95 percent). The venous lactates were 12.2 mmol per L (normal range, 0.6 to 2.4 mmol per L). After diazepam and sodium valproate infusions, the seizures stopped; PaO_2, blood pressure, and pulse normalized after endotracheal intubation, mechanical ventilation, and hydroxyethylamidon infusion. Many tablets were evacuated by gastric lavage, and activated charcoal was administered.

The serum electrolytes and liver function tests were normal. Glycemia was 7.7 mmol per L (normal range, 4.2 to 5.8 mmol per L). Serum creatinine was increased to 132 µmol per L (normal range, 40 to 100 µmol per L), with normal blood urea nitrogen. The complete blood cell count showed hyperleucocytosis to 16.6 x 10^3 µ per L (normal range, 3.6 to 10.0 10^3 µ per L) without anemia or thrombopenia. A rhabdomyolysis was found (serum creatinine kinase 1,401 U per L; normal < 195 U per L) and serum troponin was negative. The arterial blood gases improved after one hour of mechanical ventilation (pH 7.34, HCO_3^- 25.5 mmol per L, $PaCO_2$ 6.5 kPa, PaO_2 26 kPa with FiO_2 to 60 percent), and the venous lactates were restored to normal (2 mmol per L). Tests to detect antidepressants in the blood and cocaine in the urine were negative, and weakly positive for benzodiazepines and paracetamol (respectively, 98 g per L and 6.3 mg per L). The blood alcohol level test was also negative.

On admission, the electrocardiogram (ECG) showed a regular junctional rhythm (55 beats per min), an absence of P waves, and broad QRS complexes (0.16 mm per sec) with an aspect of right bundle-branch block (Figure 1).

After airway management and arterial pressure improvement, a second ECG, done 11 minutes after the first, revealed a regular sinusal rhythm (90 beats per min) with the persistence of wide QRS complexes (0.16 mm per sec) and right bundle-branch block. Four hours after the initial ECG, the cardiac rhythm was sinusal, the QRS complexes were normal (0.10 mm per sec), and the right bundle-branch block had disappeared.

The patient was quickly weaned from mechanical ventilation and extubated. He was discharged home on the fourth day of his hospitalization without complications.

Case 2

A 21-year-old drug-addicted woman was admitted for acute self-ingestion of medicines. On admission, she showed a regular respiratory rate of 12 breaths per min without pause, a blood pressure of 120/90 mmHg, and a heart rate of 84 beats per min. The patient was conscious and answered appropriately. Her pupils were slightly constricted. She acknowledged having ingested two packs of flunitrazepam, and was treated by activated charcoal. Thirty minutes after her admission, the patient was deeply asleep with no verbal response but did respond to nociceptive stimuli, and her respiratory rate remained regular (12 breaths per min). Twenty minutes later, the decrease in consciousness had advanced, and the patient was bradypneic with a respiratory rate of six breaths per min. A short-duration awakening was obtained after an intravenous injection of 0.3 mg flumazenil. Qualitative tests to detect toxic substances in the blood showed 301 mg per L of benzodiazepine and the absence of imipraminic antidepressant or neuroleptic agents.

Eight hours later the patient was sleepy, but able to be aroused; hemodynamic and respiratory indices were normal, and the pupils were constricted. Intravenous injection of 0.8 mg naloxone resulted in complete awakening and disappearance of the myosis. The patient confessed the ingestion of DP associated with flunitrazepam and also a snort of heroin: she was trying to come off heroin with these medicines. In the urine, the opiates were greater than 1,000 mg per L and there was no trace of cocaine. The presence of DP and one of its metabolites was confirmed in mass spectrometry. The initial ECG showed a first-degree auriculoventricular block (PR interval, 0.24 mm per sec) that persisted after naloxone injection. The PR interval was 0.18, then 0.16 mm per sec, respectively, 16 and 20 hours after admission. The patient was discharged home without ECG abnormality.

DISCUSSION

DP is a weak opioid analgesic that is commonly combined with other nonopioid analgesics such as paracetamol. Analgesic drugs and DP are respectively implicated in 7 percent and 4 percent of all acute self-drug poisonings in French emergency departments.[4] Fatal DP poisonings seem uncommon in France, while they are frequent in the United Kingdom and Nordic countries.[1-3] A UK study designed to assess the suicide rate due to DP-acetaminophen compound (co-proxamol) versus acetaminophen alone and tricyclic antidepressants, reported that the odds of dying after overdose with co-proxamol was 2.3 times that for tricyclic antidepressants and 28.1 times that for acetaminophen.[1] Legislation limiting the pack sizes of analgesics in the United Kingdom has been beneficial for reducing paracetamol poisoning, and the restriction of DP-paracetamol availability has also been recommended.[1,5] Moreover, it has been suggested that suicide reports where DP is in question may in fact be better categorized as accidental poisonings.[2] The Britain Committee on Safety of Medicines announced in 2005 that co-proxamol will be gradually withdrawn from the market.[6]

DP is mainly metabolized through N-demethylation into NP, a weak opioid analgesic with a significant local anesthetic effect. After repeated administration of DP, this metabolite is present in plasma in higher quantity and with a three-times-longer half-life than the parent molecule. In case of the use of great quantities of DP, as a substitute by heroin addicts or during acute intoxication, the contribution of NP to toxic effects is significant, and its long half-life can explain a prolonged action. In our observations, the addicted individuals substituted heroin for DP. It is likely that NP, because of its pharmacokinetics, has played a particular and additive role on the acute DP cardiotoxicity.[5]

Acute poisoning is characterized by a short period between the ingestion and the onset of symptoms. Toxic effects include coma, respiratory depression, myosis, and convulsions[7]; pulmonary edema, cardiogenic shock, or cardiac arrest can also occur. In a study including 222 consecutive patients hospitalized in the intensive care unit for serious acute DP intoxication over a six-year period, one-half of the patients suffered from circulatory failure at their admission, and 10 out of 17 deaths were attributed to a cardiac insufficiency[3]; ECG abnormalities were present in 41 percent of patients with widening of the QRS complex (43 patients), first-degree auriculoventricular block (1 patient), or varied ventricular arrhythmias (19 patients). Other ECG particularities have been described, such as typical bundle-branch block, widening of the QT interval, and nonspecific modifications of the T wave and ST segment. These ECG abnormalities are considered independent of all ischemic modifications secondary to respiratory failure.

Most of the toxic DP effects are linked to its opioid activities and can be reversed by opiate antagonists; the cardiac effects are apparently without link to analgesic activity. Naloxone has shown its incapacity to reverse DP cardiotoxicity[7] in vitro and in some clinical observations.[8] On isolated Purkinje fibers, DP and NP have produced a dose-dependent inhibition of V_{max}, a shortening of the action potential duration (APD), and a decrease of the effective refractory

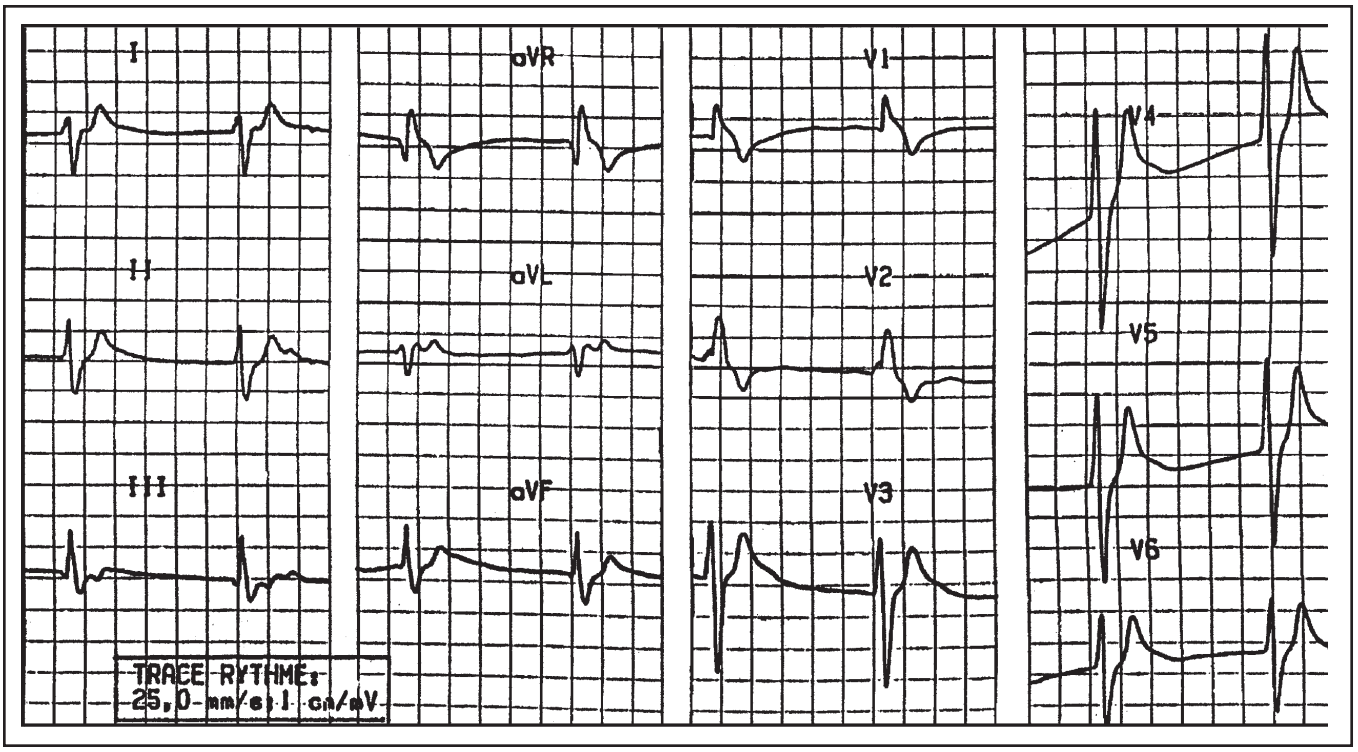

Figure 1: Dextropropoxyphene overdose, Case 1. ECG abnormalities on admission: Regular junctional rhythm (55 beats per min), absence of P waves, and broad QRS complexes (0.16 mm per sec) with aspect of right bundle-branch block.

period (ERP) without modifying the ERP/APD ratio.[9] On an isolated guinea pig atrium, they have exerted negative inotropic and chronotropic actions[9] that have been confirmed in vivo on pentobarbital-anesthetized pigs.[10,11] The depressant effect on myocardial contractility is more important with NP than with DP. Other in vivo animal experimentation has shown depressant effects on the cardiac conduction (PR interval, QRS complex and QT interval prolongation) and a biphasic effect on the cardiac frequency (bradycardia, then tachycardia).[10] DP and its metabolite have also slowed down the auriculoventricular node and His-Purkinje system conduction on endocavitary explorations.[9] Thus, it is clearly suggested that DP and NP cardiotoxicity is the result of a local anesthetic action that is twice more significant for NP.[10] Hypoxemia and lactate or respiratory acidosis that can be observed during DP poisoning are known to exacerbate the DP membrane-stabilizing effect. Whitcomb et al. have demonstrated that DP and its metabolite are a potent blocker of inward sodium currents in cardiac myocytes[12]; Ulens et al. have suggested that inward potassium current block may also contribute to the nonopioid effects of these molecules.[13] DP also exerts a negative inotropic effect by its blockage of the inward calcium current.[14] Moreover, DP and NP dilate the systemic and coronary vascular beds.[10]

The clinical use of naloxone to reverse DP cardiotoxicity is still being discussed.[8] On the isolated papillar cardiac muscle, the negative inotropic effect of DP has not been prevented by pretreatment with naloxone.[7] In an experimental study on pigs with cardiogenic shock induced by DP, naloxone led to a transitory improvement of the ejection volume that has not been reproducible with supplementary doses[11]; this action was secondary to increased cardiac frequency and myocardial contractility. Moreover, naloxone has not reversed the systemic vasodilatation after DP overdose. In healthy men or men with hypertension and who had not received opioid substances, the naloxone did not involve any modification of hemodynamic indices or catecholamine concentrations. Nevertheless, during the reversion of narcotic effects, an immediate increase of the cardiac frequency, myocardial contractility, and arterial pressure mediated by the sympathoadrenal system has been described.[15] In experimentation as well as clinical situations, naloxone does not modify ECG abnormalities, even in cases in which hemodynamic effects were reported.[8]

Animal experiments have shown the capacity of positive inotropic drugs to improve cardiovascular function during severe DP intoxication.[16] Similar results have been observed in human subjects with dopamine and dobutamine.[17] Nevertheless, arterial hypotension can resist dopaminergic and adrenergic drugs, and it has been suggested that DP has its own capacity to inhibit the calcium channels of vascular smooth muscle fibers.[12]

To summarize, the relevance of the use of naloxone in the treatment of DP-induced cardiotoxicity is still debated. Moreover, because of naloxone-induced withdrawal manifestations, its use must be circumspect in addicted

patients. Most authors have found it ineffective, and it must be emphasized that supportive therapy (e.g., mechanical ventilation, fluid replacement, inotropic drugs) is of primary importance. Gastric lavage and activated charcoal may be useful, while dialysis is of little value. No data support the use of antiarrhythmic drugs such as phenytoin or β-blockers to correct DP-induced ECG disturbances. Lidocaine has been successfully used in the management of cardiac conduction abnormalities, even though this therapeutic approach seems paradoxical because DP and lidocaine exert a common inhibition of the inward sodium currents.[12] The association of two sodium-channel inhibitors would allow the production of a less-significant sodium-channel inhibition as observed with each drug because of a difference of affinity for sodium channels. The use of sodium bicarbonate has also been reported to be successful in one case in the literature.[18]

DP has a narrow therapeutic index. Death can result from an overdose with relatively few tablets, especially when alcohol has also been taken. The rapid gastrointestinal absorption of DP explains that cardiorespiratory arrest can occur 15 minutes after an acute ingestion. Regarding fatal poisoning by DP, strict regulation in prescription with a close attention to the patient's risk category (e.g., suicidal patients, drug addicts, drinkers) is well advised.

Frédérik Staikowsky, MD, PhD, Emergency Department and SMUR, Groupe Hospitalier Sud Réunion, St. Pierre Cedex, France.
Sébastien Candella, MD, Emergency Department, CHU Tenon, Paris, France.
Maurice Raphael, MD, Emergency Department, CHIC, Montfermeil, France.

REFERENCES

1. Hawton K, Simkin S, Deeks J: Co-proxamol and suicide: A study of national mortality statistics and local non-fatal self poisonings. *BMJ.* 2003; 326(7397): 1006-1008.
2. Jonasson B, Jonasson U, Saldeen T: Suicides may be overreported and accidents underreported among fatalities due to dextropropoxyphene. *J Forensic Sci.* 1999; 44(2): 334-338.
3. Madsen PS, Strom J, Reiz S, et al.: Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand.* 1984; 28(6): 661-665.
4. Staikowsky F, Theil F, Mercadier P, et al.: Change in profile of acute self drug-poisonings over a 10-year period. *Hum Exp Toxicol.* 2004; 23(11): 507-511.
5. Hartman B, Miyada DS, Pirkle H, et al.: Serum propoxyphene concentrations in a cohort of opiate addicts on long-term propoxyphene maintenance therapy. Evidence for drug tolerance in humans. *J Anal Toxicol.* 1988; 12(1): 25-29.
6. Britain Committee on Safety of Medicines news release. Available online at: *http://www.mca.gov.uk/aboutagency/regframework/csm/csmhome.htm.*
7. Amsterdam EA, Rendig SV, Henderson GL, et al.: Depression of myocardial contractile function by propoxyphene and norpropoxyphene. *J Cardiovasc Pharmacol.* 1981; 35(1): 129-138.
8. Hantson P, Evenepoel M, Ziade D, et al.: Adverse cardiac manifestations following dextropropoxyphene overdose: Can naloxone be helpful? *Ann Emerg Med.* 1995; 25(2): 263-266.
9. Holland DR, Steinberg MI: Electrophysiologic properties of propoxyphene and norpropoxyphene in canine cardiac conducting tissues and in vivo. *Toxicol Appl Pharmacol.* 1979; 47(1): 123-133.
10. Bredgaard Sorensen M, Haggmark S, Nyhman H, et al.: Circulatory shock following intravenous propoxyphene poisoning. An experimental study of cardiac function and metabolism in pentobarbital-anesthetized pigs. *Acta Anaesthesiol Scand.* 1985; 29(1): 130-136.
11. Strom J, Haggmark S, Madsen PS, et al.: The effects of naloxone on central hemodynamics and myocardial metabolism in experimental propoxyphene-induced circulatory shock. *Acta Anaesthesiol Scand.* 1985; 29(7): 693-697.
12. Whitcomb DC, Gilliam FR, Starmer CF, et al.: Marked QRS complex abnormalities and sodium channel blockage by propoxyphene reversed with lidocaïne. *J Clin Invest.* 1989; 84(5): 1629-1636.
13. Ulens C, Daenens P, Tytgat J: Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents. *Cardiovasc Res.* 1999; 44(3): 568-578.
14. Wu C, Fry CH, Henry J: The mode of action of several opioids on cardiac muscle. *Exp Physiol.* 1997; 82(2): 261-272.
15. Kienbaum P, Thurauf N, Scherbaum N, et al.: Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor blockage in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. *Anesthesiology.* 1998; 88(5): 1154-1161.
16. Pedersen CB, Strom J, Angelo HR, et al.: Dopamine and dobutamine reduce myocardial d-propoxyphene content in experimentally intoxicated rats. *Hum Exp Toxicol.* 1991; 10(2): 109-112.
17. Krantz T, Thisted B, Strom J, et al.: Severe acute propoxyphene overdose: Plasma concentrations of propoxyphene and norpropoxyphene and the effect of dopamine on circulatory failure. *Acta Anaesthesiol Scand.* 1986; 30(4): 271-276.
18. Stork CM, Redd JT, Fine K, et al.: Propoxyphene-induced wide QRS complex dysrhythmia responsive to sodium bicarbonate. *J Toxicol Clin Toxicol.* 1995; 33(2): 179-183.