British Journal of Anaesthesia **93 (6)**: 868–71 (2004)
doi:10.1093/bja/aeh269 Advance Access publication September 17, 2004

Fulminant neuroleptic malignant syndrome after perioperative withdrawal of antiParkinsonian medication

M. Stotz[1]*, D. Thümmler[2], M. Schürch[4], J.-C. Renggli[2], A. Urwyler[1] and H. Pargger[3]

[1]Department of Anaesthesia, [2]Department of Surgery and [3]Division of Operative Critical Care, University of Basel/Kantonsspital, CH-4031 Basel, Switzerland and [4]Department of Anaesthesia, Kantonsspital Aarau, CH-5001 Aarau, Switzerland

**Corresponding author. Bloomsbury Institute of Intensive Care Medicine, University College London, Mortimer Street, London W1T 3AA, UK. E-mail: Stotzm@hotmail.com*

Neuroleptic malignant syndrome is a rare complication when using neuroleptic drugs. We report the case of a patient with severe Parkinson's disease who developed neuroleptic malignant syndrome after withdrawal of his antiParkinsonian medication for elective coronary artery bypass grafting. Sodium dantrolene may be a therapeutic option in severe cases.

Br J Anaesth 2004; **93**: 868–71

Keywords: complications, neuroleptic malignant syndrome; complications, Parkinson's disease; neuromuscular relaxant, sodium dantrolene; pharmacology, inhibitors, levodopa–benserazide; tolcapone

Accepted for publication: August 6, 2004

Neuroleptic malignant syndrome (NMS) is a rare but potentially hazardous complication when using neuroleptic drugs. We report the case of a fulminant NMS in a patient after cardiac surgery that was caused by withdrawal of his antiParkinsonian medication.

Case report

A 61-yr-old man was admitted for elective coronary artery bypass grafting (CABG). One month before, he had an inferoposterior acute myocardial infarction that, at the time, was successfully treated by thrombolysis. He still suffered from angina pectoris despite anti-ischaemic therapy with a β-blocker, angiotensin-converting enzyme inhibitor and nitrate. He also had severe Parkinson's disease, which was treated with levodopa–benserazide 250 mg and tolcapone 100 mg, both taken three times daily. Routine laboratory tests, including liver enzymes, were all within the normal range.

On the day of the operation (day 0) the patient received his regular morning medication of levodopa–benserazide and tolcapone and, for sedation, lorazepam. Thiopental was used to induce anaesthesia and pancuronium was used to facilitate endotracheal intubation. Anaesthesia was maintained with isoflurane and fentanyl. The operation, CABG using four vein grafts, and the anaesthetic course were uneventful. After the operation the patient was transferred to our intensive care unit with a low-dose norepinephrine infusion rate of 2 to 6 μg min^{-1}, which stabilized his mean arterial pressure between 70 and 80 mm Hg. His trachea was extubated 14 h after the operation. The thoracic drainage was 900 ml during the first 18 h after the operation, resulting in a haemoglobin concentration of 9.1 g dl^{-1}.

The next morning (day 1), the patient received his regular oral medication (levodopa–benserazide and tolcapone) in combination with acetaminophen, aspirin and heparin sodium. About 2 h later he became pale and sweaty, and was in distress. The mean arterial pressure fell to 55 mm Hg without tachycardia and there was no obvious bleeding. Fluid resuscitation with 500 ml of hetastarch 6% and 800 ml of lactated Ringer's solution produced no improvement. Neither increasing the norepinephrine infusion to 10 μg min^{-1} nor repeated doses of phenylephrine was effective in elevating the mean arterial pressure. An epinephrine infusion was then initiated, at a rate of 8 μg min^{-1}, and the mean arterial pressure began to improve (70 mm Hg). The haemoglobin (9.8–12.1 g dl^{-1}) and electrolyte concentrations (sodium 137–139 mmol l^{-1} and potassium 3.9–4.7 mmol l^{-1}) remained within the normal ranges, but an increasing metabolic acidosis developed despite improvement of the patient's blood pressure (for values and time course see Table 1).

Table 1 Laboratory results in a patient with fulminant neuroleptic syndrome after elective heart surgery. ABGA, arterial blood gas analysis; BE, base excess

	Day 1							Day 2				
	6:30	**15:10**	**17:00**	**17:50**	**19:00**	**20:25**	**22:50**	**0:30**	**3:30**	**7:10**	**9:50**	**14:25**
ABGA												
pH	7.41	7.22	7.02	6.93	7.1	7.11	7.09	7.21	7.26	7.37	7.49	7.51
Bicarbonate (mmol litre^{-1})	27	9	7.3	7.6	8.6	8.1	8.5	10.9	11.2	16.5	21.6	24
BE (mmol litre^{-1})	2.5	–17.4	–22.4	–24.4	–20.4	–20.7	–20.8	–16	–14.5	–7.2	–0.4	2.1
Pa_{CO_2} (kPa)	5.8	3	4	5.1	3.8	3.5	3.8	3.7	3.4	3.9	3.8	4.1
Pa_{O_2} (kPa)	16.2	25	31	36.6	28.8	13.4	20.8	18.7	18.5	19.7	27.1	19.8
Chemistry												
Na (mmol litre^{-1})				140	138					139		139
K (mmol litre^{-1})				4.6	4.8					4.5		4.5
Creatinine (μmol litre^{-1})				210	200					242		270
ASAT (U litre^{-1})				1791	2150					6596		7750
1msp; ALAT (U litre^{-1})				540	641					3711		3625
GGT (U litre^{-1})				20	20					23		24
AP (U litre^{-1})				55	52					68		82
CK (U litre^{-1})					37					621		1350

As the metabolic acidosis increased, the patient developed muscular rigidity and complained of abdominal pain. Clinical examination was indicative of peritonitis. The core body temperature was 36°C and plasma lactate was 19.0 mmol l^{-1} (normal 1.1–2.0 mmol l^{-1}). Radiographic examination of the chest showed a subdiaphragmatic air collection on the left side. An acute ruptured viscus was suspected and emergency laparotomy was performed under general anaesthesia.

General anaesthesia was induced with etomidate, and intubation of the trachea was facilitated with succinylcholine. During this procedure, the systolic arterial blood pressure fell to a minimum value of 40 mm Hg, but was restored with repeated doses of epinephrine (1 mg in total), additional fluid administration and a short period of external chest compression. Because of the patient's haemodynamic instability, anaesthesia was maintained with midazolam and fentanyl. During laparotomy, no intestinal perforation or ischaemia was found. Four tumours, each measuring 1 cm in diameter, were found on the small intestine and resected; subsequent histological examination revealed a multifocal low-grade malignant carcinoid tumour. Otherwise the anaesthetic course was uneventful, arterial pressure was maintained with continuous infusion of norepinephrine and epinephrine, and no increase in P_{CO_2} was noted during the intervention.

During surgery, repeated blood gas samples showed a worsening metabolic acidosis. Because of the patient's record of receiving tolcapone and his progressive muscle rigidity, NMS was suspected and sodium dantrolene was administered in a dose of 2.5 mg kg^{-1}. The acidosis resolved almost completely within 15 min and the patient's cardiovascular status stabilized. After the operation, mechanical ventilation was continued and the patient was transferred back to the intensive care unit. The muscular rigidity had resolved and did not return. The remaining acidosis resolved with a single adminstration of 100 ml of sodium bicarbonate 8.4%. The attending neurologist continued levodopa–benserazide therapy but withheld tolcapone after this episode.

Subsequently, the patient suffered from multiple organ dysfunction syndrome with pulmonary, hepatic, pancreatic and renal impairment. Blood cultures that were taken before the abdominal operation showed no growth of microorganisms. The creatine kinase concentration reached a maximum of 1350 U l^{-1} (normal 50–200 U l^{-1}) and the liver enzyme concentrations peaked on day 3. A needle muscle biopsy from the left lateral vastus muscle on day 4 showed no histological necrosis and appeared normal under enzyme-histochemical examination. The 5-hydroxyindoleacetic acid concentration, as a marker of the extent of the carcinoid tumour, was within the normal range. After an initial improvement of his condition, the patient died unexpectedly of acute heart failure on day 12.

The postmortem findings revealed an acute myocardial infarction. No metastases of the carcinoid tumour were detected. Brain autopsy showed numerous Lewy bodies in the neocortical region.

Discussion

The incidence of NMS is estimated to be between 0.07 and 2.2% among patients receiving neuroleptic agents,[1] with a mortality of 11%.[2] A wide variety of antipsychotic agents, including phenothiazines, butyrophenones, thioxanthenes, benzamine, clozapine and risperidone, are reported to be causal agents for eliciting NMS. It has also been reported during treatment with tolcapone in combination with clozapine[3] and also after abrupt discontinuation or reduction of antiParkinsonian medication (e.g. levodopa–benserazide and tolcapone).[4 5] The pathophysiological mechanism of NMS is unclear but is thought to be an acute dopaminergic transmission block in the basal ganglia and hypothalamus.[1] Antipsychotic agents can cause dopaminergic transmission block, and this mechanism may also occur following the

Table 2 Characteristics of neuroleptic malignant syndrome and malignant hyperthermia.*The presence of all three major criteria, or two major and four minor manifestations, indicates a high probability of the presence of neuroleptic malignant syndrome if supported by clinical history (e.g. not indicative of malignant hyperthermia)

	Neuroleptic malignant syndrome	**Malignant hyperthermia**
Clinical manifestations	Major criteria: fever, rigidity, elevated creatine kinase concentration Minor criteria: tachycardia, abnormal arterial pressure, alveolar hypoventilation and tachypnoea, altered consciousness, diaphoresis, leucocytosis*	Tachycardia, arrhythmias of all type, asystole, increased expiratory CO_2, hyperventilation, spasm of masseter muscle (trism), fever
Laboratory tests	Leucocytosis, elevated creatine kinase	Hypoxaemia, metabolic acidosis, hypercapnia, hyperkalaemia, elevated liver enzymes (transaminases) and creatine kinase
Therapy	Discontinuation of trigger; ranging from supportive therapy for mild forms to intensive care treatment; some effect of bromocriptine and amantadine reported; dantrolene for severe cases	Discontinuation of trigger; dantrolene; active cooling
Trigger	Neuroleptic drugs, antiParkinsonian medication (including withdrawal)	All volatile anaesthetics, succinylcholine
Time course	Onset reported after 24–72 h	Early onset (minutes) after trigger exposure
Diagnostic	Medical history, finally by exclusion	*In vitro* contracture test
Aetiology	Loss of regulation of central dopaminergic receptor (hypothesis: primary sympathoadrenal hyperactivity)[7]	Primary muscle defect; loss of regulation of intracellular calcium homeostasis
Genetics	Unknown	Autosomal dominantly inherited

abrupt discontinuation of neuroleptic or antiParkinsonian agents, or the use of dopamine-depleting agents.[6]

Risk factors for developing NMS are organic brain disease, mental retardation and catatonia.[7] The sympathoadrenal hyperactivity in patients seems to play a major role,[7] reflecting an imbalance in the levels of monoamine metabolites in the cerebrospinal fluid.[8] Patients with dementia of the Lewy body type, as found in the postmortem autopsy of our patient, are even more sensitive to neuroleptic medication and NMS.[9] It is not known whether patients with dementia of the Lewy body type are also more susceptible to NMS after discontinuation of antiParkinsonian medication, but it can be postulated in our case.

The diagnostic characteristics for NMS consist of major criteria (fever, rigidity and elevated creatine phosphokinase) and minor criteria (tachycardia, abnormal arterial blood pressure, tachypnoea, altered consciousness, diaphoresis and leucocytosis). The diagnosis of NMS can be difficult, as these symptoms may be missing.[10–13] In our patient, the absence of fever was misleading at the beginning of the clinical course when hypotension, increasing muscular rigidity and abdominal pain were the predominant symptoms. The clinical findings of increasing pain and acidosis, together with subdiaphragmatic air collection, led us to suspect a ruptured viscus. Subdiaphragmatic air collection may be caused by peritoneal perforation and is sometimes seen after introducing the thoracic drainage in CABG. After the exclusion of abdominal perforation, the patient's medical history, which showed discontinuation of antiParkinsonian medication, led to the diagnosis. Muscular rigidity is responsible for rhabdomyolysis and the elevation in creatine kinase concentration during NMS. We did not detect myonecrosis in the biopsy performed, but histological changes in NMS are not specific and constant.[14 15]

The specific time for development of NMS varies, and may range from hours[1] to months.[7] In our patient, the first symptoms developed 26 h after the last administration of levodopa–benserazide and tolcapone. We suggest two reasons for the early and fulminant course of the NMS in our patient. First, tolcapone is highly protein bound (>99%) and the expanded volume of distribution during cardiopulmonary bypass could have led to a rapid fall in plasma concentration. Secondly, since gastric emptying is delayed after CABG, delayed intestinal absorption of the antiParkinsonian medication after the operation on day 1 may have resulted in low plasma levels.[16] This may explain why the onset of symptoms started after the regular administration of levodopa–benserazide and tolcapone on day 1.

The clinical course of NMS is unpredictable. It can range from altered consciousness and elevated body-core temperature to myocardial infarction,[17] cardiac failure[18] and even multiple organ dysfunction. Our patient presented with vasodilation and shock of unknown origin, similar to septic shock, which was unresponsive to fluid resuscitation or to peripheral vasoconstrictors. After the exclusion of excessive blood loss with no apparent sign of bleeding and a negative chest radiograph, the muscular rigidity of the abdominal wall mimicked peritonitis which could have been an explanation for the worsening condition of the patient and led us to suspect a ruptured viscus. Finally, review of the patient's medication led to diagnosis after the intraoperative exclusion of an abdominal problem.

The treatment of NMS depends on early recognition. General treatment, including hydration, nutrition and reduction of fever, is essential; and secondary complications (e.g. hypoxia, acidosis and renal failure) must be treated aggressively. Withdrawal of the neuroleptic agent, if administered previously, is crucial. Dopamine agonists such as bromocriptine and amantadine hydrochloride have been used successfully to treat NMS. The use of glutamate receptor antagonists has also been advocated.[19] Sodium dantrolene, a non-specific direct-acting muscle relaxant used to treat

malignant hyperthermia, can also be effective in NMS; its ability to elicit muscle relaxation seems to decrease body temperature and diminish oxygen consumption. In our patient, metabolic acidosis significantly decreased after the use of sodium dantrolene and resolved with the subsequent single dose of sodium bicarbonate.

NMS occurring perioperatively may prove difficult to distinguish from malignant hyperthermia as the clinical course may be very similar (Table 2). In our case, the delay in onset of symptoms after the discontinuation of potent inhalational anaesthetics precludes malignant hyperthermia. Further differential diagnoses of NMS include neuroleptic-induced heatstroke, acute lethal catatonia, monoamine oxidase inhibitor drug interaction, central anticholinergic crisis and akinetic crisis in the advanced stages of Parkinson's disease. The akinetic crisis is characterized by severe rigidity, progressive immobilization with concomitant hyperthermia, vegetative dystonia and tachycardia. Therefore the severe form of an akinetic crisis is not easy to distinguish from NMS;[19 20] although these two entities do not differ with regard to symptoms, their therapies and clinical courses do. Akinetic crisis can develop in patients at an advanced stage of Parkinson's disease after reduction or cessation of dopaminergic therapy.[21] We postulate that the clinical course of our patient provides good evidence for NMS.

Conclusion

Withdrawal of antiParkinsonian medication in a patient with severe Parkinson's disease during elective CABG caused a fulminant NMS. Haemodynamic instability with metabolic acidosis, increasing muscular rigidity and abdominal pain were the main symptoms. Finally, after the administration of dantrolene, metabolic acidosis decreased significantly, muscular rigidity resolved and haemodynamic stability was re-established. Parkinson's disease is not a rare feature in the population scheduled for CABG; therefore clinicians must be aware of this potential complication. Perioperative continuation of antiParkinsonian medication should be considered. If levodopa–benserazide and tolcapone are to be discontinued for the operation, the dose should be reduced before the operation in a gradual manner, possibly in a clinical setting.

References

1 Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. *Br J Anaesth* 2000; **85**: 129–35

2 Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. *J Clin Psychiatry* 1989; **50**: 18–25

3 Blum M, Siegel A, Meier R, Hess K. Neuroleptic malignant-like syndrome and acute hepatitis during tolcapone and clozapine medication. *Eur Neurol* 2001; **46**: 158–60

4 Gordon P, Frucht S. Neuroleptic malignant syndrome in advanced Parkinson's disease. *Mov Disord* 2001; **16**: 960–74

5 Iwuagwu C, Riley D, Bonoma R. Neuroleptic malignant-like syndrome in an elderly patient caused by abrupt withdrawal of tolcapone, a catechol-*o*-methyl transferase inhibitor (letter). *Am J Med* 2000; **108**: 517–18

6 Toru M, Matsuda O, Makiguchi K, Sugano K. Neuroleptic malignant syndrome-like state following a withdrawal of anti-Parkinsonian drugs. *J Nerv Ment Dis* 1981; **169**: 324–7

7 Gurrera R. Sympathoadrenal hyperactivity and the etiology of neuroleptic malignant syndrome. *Am J Psychiatry* 1999; **156**: 169–80

8 Ueda M, Hammamoto M, Nagayama H, *et al*. Susceptibility to neuroleptic malignant syndrome in Parkinson's disease. *Neurology* 1999; **52**: 777–81

9 McKeith I, Fairbairn A, Perry R, *et al*. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* 1992; **305**: 673–8

10 Korn-Lubetzki I, Gottlieb S. Neuroleptic malignant syndrome with hypotonia: a diagnostic challenge. *Eur Neurol* 2001; **46**: 50–1

11 Peiris D, Seneviratne S, Wijesiriwardena B. Neuroleptic malignant syndrome without fever: a report of three cases (letter). *J Neurol Neurosurg Psychiatry* 2000; **69**: 277–8

12 Eliziade-Sciavolino C, Racco A, Proscia-Lieto T, Kleiner M. Severe hyponatremia, neuroleptic malignant syndrome, rhabdomyolysis and acute renal failure: a case report. *Mt Sinai J Med* 1998; **65**: 284–8

13 Singh R, Hassanally D. Neuroleptic malignant syndrome with normal creatine kinase (letter). *Postgrad Med J* 1996; **72**: 187

14 Kubo S, Orihara Y, Kitamura O, *et al*. An autopsy case of neuroleptic malignant syndrome (NMS) and its immunohistochemical findings of muscle-associated proteins and mitochondria. *Forensic Sci Int* 2001; **115**: 155–8

15 Behan W, Madigan M, Clark B, *et al*. Muscle changes in the neuroleptic malignant syndrome. *J Clin Pathol* 2000; **53**: 223–7

16 Schuitmaker M, Anderson B, Holford N, Woollard G. Pharmacokinetics of paracetamol in adults after cardiac surgery. *Anaesth Intensive Care* 1999; **27**: 615–22

17 Freedmann M. Neuroleptic malignant syndrome and acute myocardial infarction. case report and review. *Md Med J* 1997; **46**: 357–9

18 Benaissa M, Bekka R, Baud F. Acute cardiac failure in a case of rapidly lethal neuroleptic malignant syndrome (letter). *Intensive Care Med* 1998; **24**: 86–94

19 Kornhuber J, Weller M, Riederer P. Glutamate receptor antagonists for neuroleptic malignant syndrome and akinetic hyperthermic Parkinsonian crisis. *J Neural Transm Park Dis Dement Sect* 1993; **6**: 63–72

20 Nierenberg D, Disch M, Manheimer E, *et al*. Facilitating prompt diagnosis and treatment of the neuroleptic malignant syndrome. *Clin Pharmacol Ther* 1991; **50**: 580–6

21 Bachli E, Albani C. Akinetic crisis in Parkinson's disease. *Schweiz Med Wochenschr* 1994; **124**: 1017–23