Neuroleptic malignant syndrome

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Neuroleptic malignant syndrome (NMS) is a relatively rare but potentially fatal complication of the use of neuroleptic drugs. It was first described by Delay and colleagues after the introduction of neuroleptics in 1960; they called it 'akinetic hypertonic syndrome'.[16] Over the last decade, almost 1000 cases of NMS have been reported, but many features of this syndrome remain controversial. Indeed, a graded scale of specific signs and symptoms for the diagnosis of NMS and a spectrum of clinical severity are two issues that await resolution.[1 22] Many diagnostic criteria have been proposed, but no single set of criteria has been adopted for general use. Different presentations of this disorder could explain some of the contradictory findings associated with NMS; these include the following: (i) prospective studies have provided disparate estimates of the frequency of NMS, ranging from 0.07%[20] to 2.2%[26] among patients receiving neuroleptic agents; (ii) risk factors for NMS vary in different patient populations;[29] and (iii) the association between NMS and other potentially fatal syndromes, such as malignant hyperthermia, is unclear.

Pathogenesis of NMS

Two major, though not necessarily competing, theories to explain NMS are a neuroleptic-induced alteration of central neuroregulatory mechanisms and an abnormal reaction of predisposed skeletal muscle. This latter hypothesis is based on similarities between NMS and malignant hyperthermia and suggests that neuroleptic medications induce abnormal calcium availability in muscle cells of susceptible individuals and trigger muscle rigidity, rhabdomyolysis and hyperthermia. Alternatively, in some circumstances, it is possible that neuroleptics could be directly toxic to normal skeletal muscle.

Central dopamine receptor blockade

Dopamine plays a role in central thermoregulation in mammals. A dopamine injection into the preoptic–anterior hypothalamus causes a reduction in core temperature.[14] Since neuroleptic drugs block dopamine receptor sites, the hyperthermia associated with NMS may result from a blockade of hypothalamic dopamine sites. This was suggested 20 yr ago by Henderson and Wooten, who reported a patient with Parkinson's disease and chronic psychosis who developed NMS when dopaminergic agonists were withdrawn but haloperidol was continued.[24] NMS has also been observed in a patient with Huntington's chorea taking methyltyrosine, a cathecholamine synthesis inhibitor, and tetrabenazine, which depletes central nervous system catecholamines.[10] This suggests that NMS is caused by dopamine depletion or blockade, leading to abnormal central thermoregulation. The dopamine blockade theory is supported by the report of a case in which NMS developed when L-dopa/carbidopa and amantadine were abruptly discontinued in a patient with Parkinson's disease who had never taken neuroleptics.[50] Some dopamine-function-enhancing drugs, such as bromocriptine[9] or amantadine,[36] have shown efficacy in treating NMS.

The blockade of dopamine receptors in the hypothalamus is thought to lead to impaired heat dissipation. In addition, blockade of dopamine receptors in the corpus striatum is thought to cause muscular rigidity, generating heat. The excess heat production, in association with a decrease in heat dissipation, produces hyperthermia, which is one of the main signs of the syndrome. The peripheral anticholinergic effects of neuroleptics which reduce sweating probably do not play a major role in hyperthermia associated with NMS since most NMS patients (70%) are in a sweat. However, it is unlikely that blockade of dopamine receptors in the hypothalamus and corpus striatum could completely explain all the signs of NMS. Indeed, hypothalamic thermoregulation involves noradrenergic, serotoninergic, cholinergic and central dopaminergic pathways.[7] Many neuroleptics may have additional selective effects on peptides co-transmitting with dopamine in the striatum and other parts of the brain.

Primary skeletal muscle defect similar to malignant hyperthermia

A common pathophysiology of NMS and malignant hyperthermia has been suggested.[15 17 49] This hypothesis is based mainly on three points: (i) NMS and malignant hyperthermia have clinical features in common, including hyperthermia, rigidity, an elevated creatine kinase concentration and a mortality rate for both NMS and malignant hyperthermia of 10–30%; (ii) sodium dantrolene, a peripheral muscle relaxant, has been used successfully in both syndromes; (iii) abnormal results have been found in *in vitro* contractility tests in patients with NMS or malignant hyperthermia. These *in vitro* halothane–caffeine tests are at present the most reliable diagnostic measure for patients susceptible to malignant hyperthermia.[47] They determine the sensitivity of muscle fibres to halothane or caffeine added to the bathing solution. Muscle fibres from patients susceptible to malignant hyperthermia contract in response to these drugs at a lower concentration than those from normal patients. Hence, in order to evaluate a possible association between NMS and malignant hyperthermia, several investigators have used such tests on skeletal muscle fibres removed from patients with documented NMS episodes. However, conflicting results have been reported regarding the prevalence of malignant hyperthermia susceptibility among NMS patients.[2 5 13] Three main series and some sporadic case reports have been published. Caroff and colleagues[13] found that five of seven NMS patients were susceptible to malignant hyperthermia on the basis of a 3% halothane response. Araki and colleagues[5] showed, using a caffeine skinned fibre technique, that there was abnormal contracture in six NMS patients similar to that seen in malignant hyperthermia. Our laboratory[2 32] found that 13 of 14 NMS patients were not susceptible to malignant hyperthermia and the other was equivocal.

One possible explanation for these discrepancies is that patients diagnosed as having NMS may be a heterogeneous group with great variability in clinical presentation, response to treatment and, possibly, response to test drugs. Some of the variation in the *in vitro* results from different centres may be attributable to variations in laboratory procedures. The variety of tests used for diagnosing malignant hyperthermia diagnosis included using caffeine alone,[5] halothane and caffeine on separate muscle bundles,[32] halothane with cumulative concentrations of caffeine,[49] or caffeine on skinned muscle fibres.[5] The sensitivity of this latter method may be inadequate as the technique itself excludes any detection of a possible defect in the sarcolemma.[4] Differences were also observed in the criteria used for diagnosing malignant hyperthermia based on *in vitro* contracture tests:[13] some centres used the development of a contracture of >0.5 g force in response to 1% halothane as a threshold while others chose >0.7 g force in response to 3% halothane. The European malignant hyperthermia group[17] required, for an abnormal response to halothane, a contracture of $\geqslant$0.2 g force in response to <2% halothane. In other sporadic case reports, the protocol and diagnostic criteria were not fully explained.

The time interval between adverse reaction to the neuroleptic drug and the biopsy was either not specified,[5] or was 1 month[13] or 2–3 weeks.[2 32] Caroff and colleagues[13] found no correlation between the maximum halothane response and the time between normalization of creatine kinase concentration and biopsy. However, contracture test results in NMS patients may be falsely positive and reflect coincidental changes in muscle resulting from NMS. For example, Gallant and colleagues[19] reported that muscle fibre injury during biopsy and *in vitro* testing procedures enhances halothane sensitivity and could contribute to false-positive contracture test results. Denborough, Collins and Hopkinson[17] reported positive results in two patients who recovered from non-drug-related episodes of rhabdomyolysis. Adnet and colleagues[3] found that if cut fibre specimens depolarize with time after biopsy, these preparations become less sensitive to caffeine, and so one must be cautious when interpreting the results of *in vitro* caffeine contracture test. This suggests that non-specific muscle damage secondary to metabolic factors, drug exposure, abnormalities in central nervous system activity or testing procedures may have contributed to the abnormal responses observed *in vitro* in muscle obtained from survivors of NMS episodes. Since our previous reports, 19 additional patients have been investigated according to the European malignant hyperthermia protocol. None of these patients were susceptible to malignant hyperthermia and two patients were equivocal. Statistical analysis for inferences based upon negative results can be performed. The increase in our study group size from 14 to 33 patients decreases the likelihood of malignant hyperthermia occurring in NMS patients from 31% to <10% with 95% confidence. Our study does not justify abandoning precautions against malignant hyperthermia in NMS patients. Mathematical analysis suggests that 59 consecutive NMS patients would have to test negative, with a similar *in vitro* protocol, in order to exclude statistically any cross-reactivity between malignant hyperthermia and NMS. Until such results are available, we suggest that all patients with clinical NMS should be tested for susceptibility to malignant hyperthermia before being considered at risk of this disorder during anaesthesia.

Direct toxic effect on skeletal muscle induced by neuroleptics

Muscle contracture has been induced *in vitro* by neuroleptic agents such as chlorpromazine.[31] The drug is reported to influence calcium ion transport across the sarcoplasmic reticulum, and has been studied in various experimental muscle preparations. In a study on skinned fibres, chlorpromazine influenced both the contractile system and the function of the sarcoplasmic reticulum.[45] However, it has been shown previously that the drug induced contracture

to the same extent in both NMS and normal muscle.[2] Likewise, Caroff and colleagues[13] also found no significant differences in the muscle response to another neuroleptic drug, fluphenazine, between NMS, malignant hyperthermia-susceptible and control patients.

To explore further a possible direct action of neuroleptic drugs on skeletal muscle, we analysed the *in vitro* muscle contracture response to four neuroleptic agents implicated in NMS episodes.[40] Muscle from NMS patients was no more sensitive to neuroleptic drugs than muscle from normal patients. These negative findings may indicate that the *in vitro* contracture response to neuroleptic agents does not correlate with clinical evidence of NMS. However, this may also show that neuroleptics are potentially active on skeletal muscle. Thus, it is possible that, in some circumstances, such as exhaustion, psychomotor agitation or dehydration, which are not explored by the *in vitro* method, neuroleptics may be toxic to skeletal muscle, leading to contracture and rhabdomyolysis. Therefore, neuroleptic contracture tests may not adequately reproduce conditions *in vivo*. Many factors present *in vivo*, such as neuroleptic metabolites, central dopaminergic blockade and risk factors for NMS, should be taken into consideration in developing more precise pharmacological models to explore possible interactions between neuroleptics and skeletal muscle function. Of particular interest is the fact that rechallenge with the original agent may not result in a recurrence of NMS. This suggests that neuroleptics may be a necessary, but not exclusive, cause of the syndrome.[12 34]

In vivo *experimental model for NMS*

Very recently, an experimental model for NMS has been developed. Rabbits treated with haloperidol and exposed to high ambient temperature may be useful in elucidating the pathogenesis of NMS.[46]

Molecular basis of NMS

The molecular basis for NMS is unclear, but studies suggest that genetic factors are involved in its pathogenesis.[27] Involvement of the serotonergic system in NMS has been suggested, but polymorphisms in the 5-HT1A and 5-HT2A receptor genes do not determine susceptibility to NMS.[28] Other studies do not support an association between NMS and the mutations in the ryanodine receptor gene reported with malignant hyperthermia.[38]

Clinical features

NMS typically develops over a period of 24–72 h but many investigators have described a more insidious evolution of symptoms. The risk of developing NMS has been reported to last for 10–20 days after oral neuroleptics are discontinued and even longer when associated with depot forms of the drugs. Consistent diagnostic criteria have been used only in some clinical studies.[29–31] Three major symptoms indicate a high probability of the presence of NMS: hyperthermia, rigidity and an elevated creatine phosphokinase concentration, reflecting rhabdomyolysis[34] (Table 1). In the absence of these criteria, the diagnosis of NMS should be questioned, since other symptoms of the disorder may be seen in patients taking neuroleptics without having NMS. Elevated temperature (≥38.5°C) in the absence of other systemic illness is observed in most patients. Muscle rigidity consists of a generalized 'lead pipe' increase in tone which may result in decreased chest-wall compliance with resulting tachypnoeic hypoventilation and pulmonary infection secondarily. This increase in muscle tone may be accompanied by extrapyramidal symptoms including dyskinesia, dysarthria or Parkinsonism. The creatine phosphokinase concentration is always elevated (>1000 IU litre^{-1}), reflecting myonecrosis secondary to intense muscle contracture. This often results in acute myoglobinuric renal failure. Minor signs alone do not indicate a high probability of NMS. Diaphoresis, tachycardia and abnormally high arterial pressure are common signs of autonomic dysfunction. Altered consciousness ranges from agitation to stupor or coma. Many other clinical signs of lesser frequency have been reported, including opisthotonos, grand mal seizures, Babinski's signs, chorea and trismus.

Table 1 Criteria for guidance in the diagnosis of neuroleptic malignant syndrome. The presence of all three major, 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) (from reference 34)

Category	Manifestations
Major	Fever, rigidity, elevated creatine phosphokinase concentration
Minor	Tachycardia, abnormal arterial pressure, tachypnoea, altered consciousness, diaphoresis, leucocytosis

Leucocytosis, ranging from a slight elevation to 30 000 mm^{-3}, is the only frequent laboratory finding included in the minor signs of NMS. Other non-specific laboratory abnormalities have been reported, such as mildly elevated hepatic enzymes (transaminase, lactic dehydrogenase and alkaline phosphatase). Non-specific encephalopathy may occur. Lumbar puncture should be done for the differential diagnosis but is usually normal in NMS. Cerebral CT scan is normal; non-specific changes are usually observed in muscle biopsy or post-mortem histopathological studies of the brain.

Some authors are in favour of an approach whereby a diagnosis of NMS is only made if certain signs are present. For example, Levenson[34] suggests that the presence of all three major, or two major and four minor signs (Table 1) indicates a high probability of NMS. These criteria for guidance in the diagnosis of NMS are commonly used in clinical research studies.[2 13] Similarly, Pope, Keck and

McElroy[39] have published 'definite' and 'probable' criteria for NMS. Others still prefer to think in terms of a spectrum of neuroleptic-related neurotoxicity, with varying combinations that enhance the potential for inappropriate diagnosis or management.[35]

A decrease in mortality from NMS has been reported in recent years. NMS resulted in a 76% mortality before 1970, a 22% mortality from 1970 to 1980, and a 15% mortality since 1980. Shalev, Hermesh and Munitz[44] reported a significant decrease in mortality since 1984 (to 11%), which occurred independently of the treatment used: dopamine agonist or dantrolene. Renal failure is a strong predictor of mortality, representing a mortality risk of approximately 50%.

Medications and risk factors

A wide variety of antipsychotic agents is associated with this syndrome, including phenothiazines, butyrophenones, thioxanthenes, benzamides and miscellaneous novel antipsychotic agents such as clozapine and risperidone.[23] Other circumstances, such as abrupt discontinuation of neuroleptic or antiparkinsonian agents, and the use of dopamine-depleting agents, have also been reported to produce NMS. The onset of the syndrome is not related to the duration of exposure to neuroleptics or to toxic overdose. All ages (including children) and both genders are affected in NMS but young adult males predominate among reported cases. Cases have been reported in both psychiatric and medical patients including after multiple trauma or preoperative use of neuroleptic agents. Alcoholic patients are at greater risk of developing NMS during treatment of delirium or its prevention by droperidol or tiapride.[2] Abnormalities of muscle metabolism in alcoholic patients are caused by ethanol toxicity and malnutrition.[8] This may sensitize the muscle to the action of neuroleptics. In a psychiatric population, several studies[6 30 42] showed that patients with NMS displayed significantly greater psychomotor agitation, received significantly higher doses of neuroleptics at greater dose increments, and received more intramuscular injections than other patients having similar medication without evidence of NMS. Many authors have pointed out that most cases have occurred in patients receiving haloperidol or, to a lesser extent, depot fluphenazine. These clinical observations do not necessarily mean that the two drugs carry a higher risk of causing NMS. One must consider the frequency with which the drug is prescribed: haloperidol is one of the most commonly used medications. Furthermore, sicker patients are more likely to receive haloperidol or fluphenazine than other neuroleptics. Sicker patients may also be at higher risk of NMS because of greater likelihood of dehydration, exhaustion or malnutrition.[11 12 34] Other suggested predisposing factors include infection, concurrent organic brain disease or sympathoadrenal hyperactivity.[21]

Differential diagnosis

Patients on neuroleptics who develop hyperthermia, muscle rigidity and autonomic dysfunction should have all psychotropic medications withdrawn immediately until rigorous diagnostic investigation reveals a specific aetiology. Disorders that can be mistaken for NMS include rhabdomyolysis from other causes, central nervous system infections, a cerebral mass, tetanus and lithium toxicity. Other specific illnesses should be considered in the differential diagnosis of NMS, including neuroleptic-related heat stroke, catatonia, drug interactions with monoamine oxidase inhibitors, the central anticholinergic syndrome and anaesthetic-induced malignant hyperthermia. In order to make a diagnosis, the physician who is evaluating a patient with suspected NMS should carry out the following tests in addition to a careful history and physical examination: creatine phosphokinase concentration; white blood cell count; renal function; EEG; CT scan; lumbar puncture; and serum lithium concentration.

Neuroleptic-induced heat stroke

Classic heat stroke is a life-threatening condition in which heat gain from metabolism and the environment exceeds heat loss by evaporation and convection. Neuroleptics predispose to hyperthermia by their anticholinergic properties, which block sweating and heat dissipation, and by their antidopaminergic properties, which interfere with hypothalamic thermoregulation. Contributing factors include hot, humid weather and excessive agitation or exercise not accompanied by adequate fluid intake. When an acutely catastrophic disorder associated with hyperthermia and altered consciousness develops in a patient taking neuroleptics, early differential diagnosis between NMS and neuroleptic-induced heat stroke is imperative if potentially life-saving treatment, which differs according to the condition, is to be given promptly. Neuroleptic-induced heat stroke can be differentiated from NMS by abrupt onset, often with seizures, the absence of extrapyramidal signs, absence of sweating, and a history of physical exercise or exposure to high ambient temperature.[33] Heat stroke needs rapid, effective cooling methods initiated as early as possible with continuous monitoring of the core temperature and vigorous fluid replacement for both rehydration and a more rapid reduction in temperature.

Acute lethal catatonia

Lethal catatonia is a very rare psychiatric syndrome that shares some features with NMS, including hyperthermia, akinesia and muscle rigidity. Catatonic states as a result of severe akinesia are most common in patients on neurolep-

tics. Since laboratory findings, CT scans, EEGs and other somatic data have not yet been of value in differentiating the two conditions, the diagnosis requires careful detailing of the patient's condition in the preceding 2–3 weeks.[18] The catatonic syndrome may be preceded by emotional withdrawal, depressive symptoms, neglect of previous hobbies, anxiety symptoms or acute agitation. These signs do not differ from those of other patients with schizophrenia but they seldom last for >2 weeks. The complete picture is more likely to involve choreiform sterotypy, primitive hyperkinesias, torsion spasms and rhythmic circling movements of the arms. Death may result from respiratory arrest or cardiovascular collapse.

Drug interactions with monoamine oxidase inhibitors

Agitation, delirium, hyperthermic reactions and death have been described as adverse effects of monoamine oxidase inhibitors in combination with narcotic drugs or tricyclic antidepressants. It has been suggested that the amine reuptake inhibitory properties of tricyclic antidepressants could interact dangerously with the sympathomimetic properties of monoamine oxidase inhibitors. Similar signs may be seen with overdosage of monoamine oxidase inhibitors. Patients taking neuroleptics may also be receiving treatment with monoamide oxidase inhibitors.

Central anticholinergic syndrome

Peripheral signs of atropine poisoning characterize the syndrome, including dry skin, dry mouth, dilated pupils and urinary retention. The patient is usually confused and disorientated (anticholinergic delirium) and the temperature is often elevated. Physostigmine may induce a resolution of symptoms that is not observed in NMS.

Treatment

Successful treatment of NMS depends on early clinical recognition and prompt withdrawal of the neuroleptic agents. Neuroleptics cannot be removed by dialysis, and blood concentrations decline only slowly. General symptomatic treatment, such as hydration, nutrition and reduction of fever, is essential. Secondary complications, such as hypoxia, acidosis and renal failure, must be treated aggressively. Low-dose heparin seems to be indicated to prevent venous thrombosis in an immobilized patient. Other dopamine antagonists, such as metoclopramide, should be avoided. In Caroff's review of 60 cases,[12] supportive therapy was the predominant treatment modality. The benefit of adding specific therapies to supportive measures is still debated. Insufficient data are available to evaluate the efficacy of specific treatments reported in the literature. Potential benefits from their use cannot, therefore, be excluded. Only one study evaluated treatment options for NMS.[41] In a series of 64 cases derived from an extensive review of the literature, 11 patients received only supportive therapy. The others received additional therapies including dantrolene (14 patients), bromocriptine (22 patients), benzodiazepine (one patient) and combinations of the above (nine patients). Efficacy was evaluated in each case by determining the delay in the clinical response and time to complete recovery. Therapy with bromocriptine (5 mg orally or nasogastrically four times daily) was effective after approximately 1 day. This was significantly more rapid than that achieved by supportive therapy alone. Complete resolution was achieved more quickly with bromocriptine (10 days) or dantrolene (9 days; 2–3 mg kg^{-1} day^{-1} i.v. without exceeding 10 mg kg^{-1} day^{-1}) than with supportive therapy (15 days).

The place of sodium dantrolene, the drug of choice for malignant hyperthermia, is less well defined in the treatment of NMS. Sodium dantrolene inhibits calcium release from the sarcoplasmic reticulum, decreasing available calcium for ongoing muscle contracture. The drug is a non-specific, directly acting muscle relaxant and a decrease in body temperature coincides with muscle relaxation. Oxygen consumption diminishes and heart rate and respiratory rate decrease correspondingly. It has been suggested that the initial dosage should be 2 mg kg^{-1} given intravenously.[15] This dose may be repeated every 10 min, up to a total dose of 10 mg kg^{-1} day^{-1}. The oral dosage has ranged from 50 to 200 mg day^{-1}. Hepatic toxicity may occur with doses of >10 mg kg^{-1} day^{-1}.

Bromocriptine mesylate, a dopamine agonist, is also used to treat NMS.[9] Bromocriptine doses have ranged from 2.5 to 10 mg four times a day. Hypotension is the most limiting side-effect. The drug seems to be well tolerated by psychotic patients even though it is a strong central dopamine agonist. Rigidity may begin to decrease during the first few hours followed by a decrease in temperature, along with normalization of arterial pressure. This effect on rigidity and tremor strengthens the hypothesis of a dopamine-receptor blockade in NMS. Bromocriptine and dantrolene have been used together without complications.[41]

Another dopamine agonist, amantadine hydrochloride, has been used successfully in some cases.[36] Levodopa, combined with the dopadecarboxylase inhibitor carbidopa, has also been reported to be effective in reversing hyperthermia.[24] Treatment may have to be continued for several days. Anticholinergic drugs, such as benzatropine, usually do not reduce the rigidity of NMS and do not affect hyperthermia. Benzodiazepine derivatives, which enhance GABA-ergic function, have caused transient decreases in symptoms. In every case, these drugs are recommended to control 'agitated' patients being treated for NMS. Carbamazepine has been used successfully in two patients: NMS completely resolved within 8 h.[48]

Electroconvulsive therapy (ECT) has improved some of the syndrome's components, notably fever, sweating and level of consciousness.[25]

Recurrence of neuroleptic malignant syndrome

Since many patients with NMS are schizophrenics, they require further neuroleptic treatment in the course of their illness, often very soon after the onset of NMS. Rechallenge with drugs of the same milligram potency as the original stimulus in six patients resulted in recurrent NMS in five of the six patients, with two deaths. Rechallenge with less potent antipsychotics, such as thioridazine, was safe in nine of 10 cases.[44] McCarthy[37] reported a fatal case of neuroleptic syndrome after a milder episode 3 months earlier. The safest approach for prevention of recurrence is a regimen where doses of a low-potency neuroleptic are increased very slowly. Substitute treatments, such as lithium carbonate or ECT, may offer a safe alternative to those patients who respond to these treatments. Prevention of NMS awaits better understanding of the underlying pathophysiology. Of prime importance seems to be the avoidance of marked dehydration in neuroleptic-treated patients; this may reduce the prevalence and morbidity of the syndrome.

Electroconvulsive therapy in patients with a history of NMS

Since a common pathophysiology has been suggested between NMS and malignant hyperthermia,[17 49] the possibility that patients with a history of NMS may be vulnerable to developing malignant hyperthermia is an important factor when considering general anaesthesia, especially succinylcholine administration immediately before electrical stimulation for ECT. To date, there is no report in the literature of malignant hyperthermia as a complication of ECT in NMS patients. One study[25] found that none of the patients who had NMS and underwent ECT, nor their relatives who had also undergone ECT, had any malignant hyperthermia-like symptoms or other secondary effects despite repeated use of succinylcholine in all cases. The authors reported a total of 147 i.v. administrations of succinylcholine in a dose range of 15–30 mg in 12 patients without any complication. These results are consistent with sporadic reports of the safe use of ECT for patients with NMS (see reference 25 for review).

ECT with the use of succinylcholine, which is an effective and rapid mode of treatment for cases of NMS unresponsive to supportive medical therapy, is not, therefore, contraindicated. However, until the association, between NMS and malignant hyperthermia is conclusively disproved, careful metabolic monitoring of general anaesthesia is necessary.

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