CASE REPORT

Transient bradycardia induced by thiopentone sodium: a unique challenge in the management of refractory status epilepticus

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SUMMARY

Thiopentone sodium is one of the important drugs in the armamentarium for terminating refractory status epilepticus, a neurological emergency. We report a case of thiopentone-related bradycardia during the management of the new onset refractory status epilepticus in a young man, which was circumvented by prophylactic insertion of temporary pacemaker while thiopentone infusion was continued. A systematic approach was employed to manage the status epilepticus, including infusion of thiamine and glucose followed by antiepileptic drugs. The patient was ventilated and infused with lorazepam, phenytoin, sodium valproate, levetiracetam and midazolam followed by thiopentone sodium. With the introduction of thiopentone the seizures could be controlled but the patient developed severe bradycardia and junctional rhythm. The bradycardia disappeared when thiopentone was withdrawn and reappeared when the drug was reintroduced. Propofol infusion was tried with no respite in seizures. Later thiopentone sodium was reintroduced after inserting temporary cardiac pacemaker. Seizure was controlled and patient was weaned off the ventilator.

BACKGROUND

Status epilepticus (SE) is a neurological emergency. Existing guidelines recommend a protocol-based systematic approach, emergency investigations such as electrolytes and blood glucose, use of intravenous glucose and thiamine, correcting metabolic abnormalities, initiation and maintenance of antiepileptic drugs (AED), attention to hypotension, cardiac dysrhythmia, hyperthermia, lactic acidosis, rhabdomyolysis and cerebral oedema. A typical protocol for emergency drug use involves lorazepam for early SE; phenytoin, fosphenytoin or phenobarbitone for established SE and anaesthesia with either thiopentone or propofol for refractory SE.[1] Intravenous sodium valproate is also increasingly being used for established SE.[2] The new onset refractory status epilepticus (NORSE) is a recently defined neurological entity, with high mortality.[3] We describe a unique case of thiopentone-related bradycardia, without dyskalaemia during the management of NORSE in a young man, which was circumvented by prophylactic insertion of temporary pacemaker while thiopentone infusion was continued. Such complication of thiopentone infusion has hitherto not been described.

CASE PRESENTATION

A 30-year-old man was admitted with a history of low-grade fever for 2 days followed by frequent, recurrent generalised tonic clonic seizures, culminating into SE. He was not a known epileptic patient. There was no history of alcoholism, head injury, focal sensorimotor weakness or any major neurological illness in past. Examination revealed him to be febrile and continually convulsing, without recovery of consciousness in between seizures. Blood pressure (BP) and respiration were normal. There were no signs of meningeal irritation, jaundice, petechial haemorrhages or splenomegaly.

INVESTIGATIONS

- Random blood sugar, serum electrolytes
- Peripheral smear and antigen tests for malaria
- Cerebrospinal fluid analysis including herpes simplex virus (HSV) PCR ,tests for mycobacteria, fungi and spirochetes
- Contrast-enhanced CT scan and MRI of the brain
- Doppler venography

TREATMENT

An intravenous line was established and intravenous glucose and thiamine was administered, pending report of blood sugar and electrolytes which subsequently turned out to be normal. Malaria antigen test and smear were negative. He was admitted to the neurology intensive care unit with provisional diagnosis of encephalitis with SE. Prompt sequential protocol-based treatment with intravenous lorazepam (4 mg), phenytoin sodium (1000 mg), sodium valproate (1500 mg) and levetiracetam (2000 mg) was administered, with no respite in seizures. SE persisted even after addition and titration of midazolam to the maximum possible dose, after endotracheal intubation and elective ventilation. Intravenous acyclovir and ceftriaxone were started pending the results of cerebrospinal fluid (CSF) HSV PCR and MRI of the brain.

In view of uncontrolled seizures, intravenous thiopentone sodium 100 mg bolus followed by 100 mg/h infusion was started, leading to prompt resolution of SE. However, within a few minutes, patient developed sinus bradycardia, deteriorating into junctional escape rhythm within an hour (figure 1A). BP remained normal. Serum electrolytes, including potassium levels, were normal. Thiopentone was subsequently withheld, in view of

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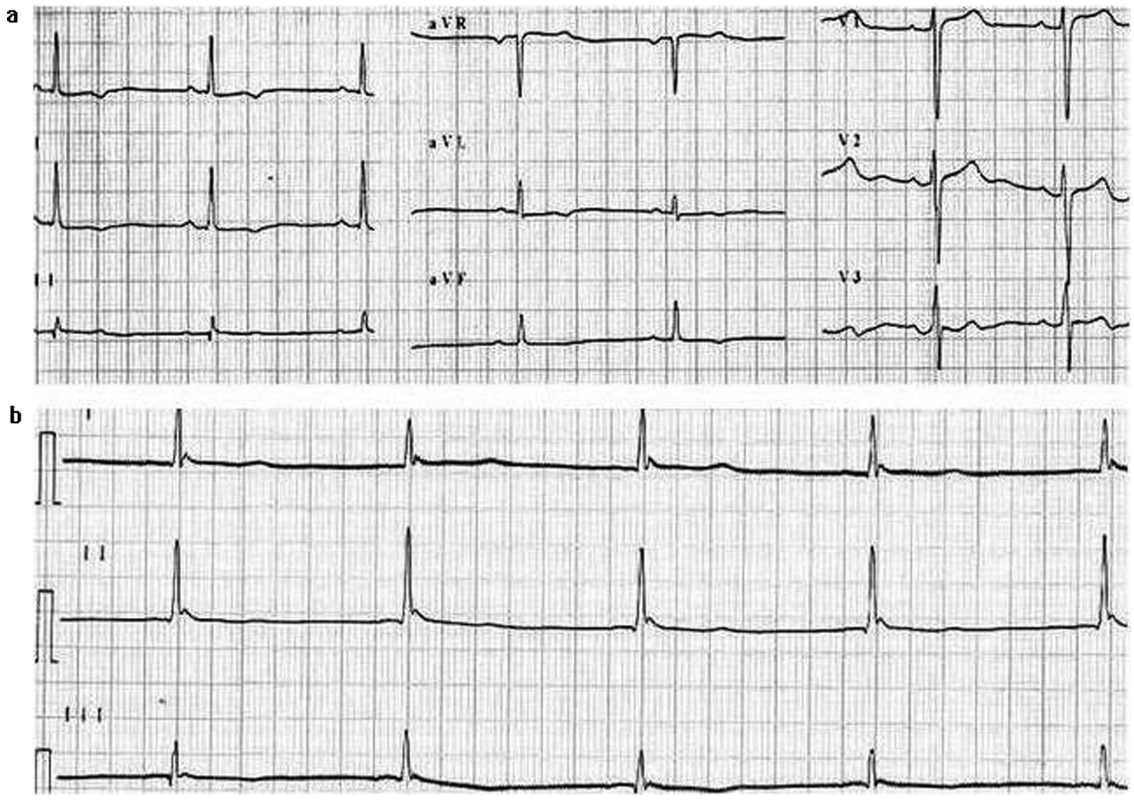

Figure 1 Reversible ECG abnomalities during thiopentone infusion: (A) sinus bradycardia during first trial. (B) Junctional escape rhythm on second trial. Both patterns reversed to normal sinus rhythm on discontinuation of thiopentone.

strong temporal correlation between starting of thiopentone infusion and subsequent bradyarrythmia and no other cause having been discerned for the latter. Over the ensuing hour, heart rate picked up and ECG revealed a normal sinus rhythm at 70/min, albeit with return of seizures. Thiopentone rechallenge at a rate of 50 mg/h intravenous infusion was tried but had to be given up since bradycardia resurfaced within minutes, deteriorating again within an hour to junctional escape rhythm (figure 1B). BP and serum potassium remained normal. Once again, bradycardia rapidly disappeared after discontinuation of thiopentone infusion, further supporting the possibility of bradycardia to be a complication of thiopentone infusion. Intravenous propofol 50 mg bolus followed by 50 mg/h was subsequently started. However, seizures continued to occur intermittently despite escalation of propofol up to 10 mg/kg/h and addition of multiple maintenance AEDs including levetiracetam 2500 mg/day, carbamazepine 1200 mg/day, clobazam 40 mg/day, topiramate 200 mg/day, lacosamide 200 mg/day and zonisamide 100 mg/day, through Ryle's tube. Tracheostomy had been performed after 48 h of endotracheal intubation and patient was maintained on mechanical ventilation. Brain CT revealed calcification of the right basal ganglia. MRI of the brain, including contrast and MR venogram was normal except for calcification in the right basal ganglia (figure 2). CSF analysis revealed no

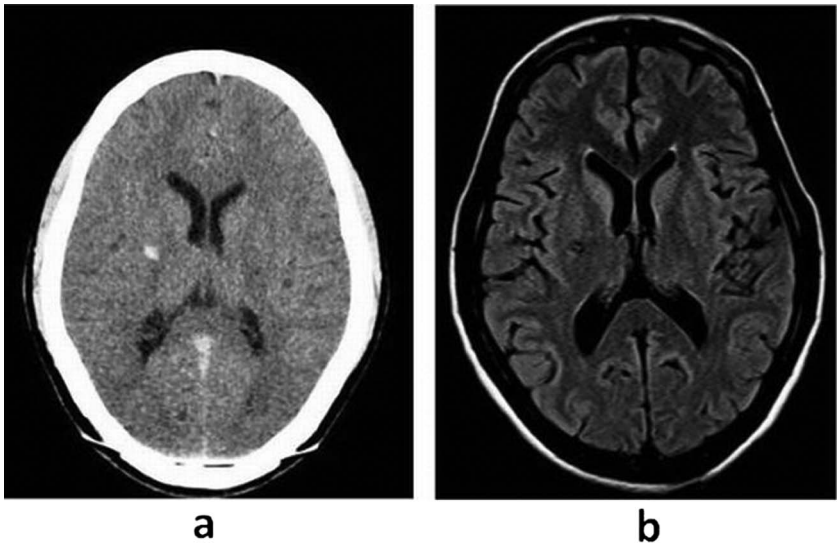

Figure 2 Right basal ganglia calcification evident on cerebral imaging (A) as hyper density in CT scan (B) as hypointensity in MRI of the brain (axial FLAIR sequence).

pleocytosis and normal biochemical and microbiological profile, including HSV PCR, fungal, mycobacterial and spirochetes workup. The clinical course was also complicated by right subclavian and jugular deep venous thrombosis secondary to inserted subclavian central venous line, which was suspected due to right upper limb oedema and confirmed by compression ultrasonography and Doppler venography. Thrombosis was managed successfully with therapeutic doses of fractionated heparin. Left-side veins were normal. Besides, 8 days of continuous high-dose propofol infusion led to hypertriglyceridaemia (1500 mg/dL), though acid–base status remained normal. On the ninth day, the patient deteriorated again, with several episodes of seizures on a single day. Metabolic causes were ruled out by appropriate investigations. We were confronted with a unique situation, wherein majority of the drugs were ineffective and the only effective drug (thiopentone) caused significant, possibly life-threatening adverse drug reaction of bradyarrythmia. It was felt that thiopentone could be used for a short period to control SE provided the bradycardia was prevented. A novel therapeutic strategy was then planned. With the cardiologist's help, thiopentone infusion was restarted under cover of temporary prophylactic pacemaker implanted in the right ventricle through left subclavian venous access (figure 3).

OUTCOME AND FOLLOW-UP

Prophylactic pacemaker made it possible to continue thiopentone and achieve an excellent control of seizures; subsequently propofol was tapered and stopped over next 2 days. There was no recurrence of bradycardia. Thiopentone infusion had to be continued over next 4 days, after which it was gradually tapered and stopped over the ensuing 3 days. Patient remained seizure free thereafter and gradually regained sensorium. He was weaned off mechanical ventilation over the next 4 days and made a steady recovery thereafter. No residual sensorimotor deficits were observed. He was discharged on three AEDs and at 3 months after discharge he is still on these drugs.

DISCUSSION

SE not responding to first-line and second-line anticonvulsant therapy is considered to be refractory status epilepticus (RSE).[4] Wilder-Smith *et al*[3] described the syndrome of NORSE in a series of seven patients characterised by female gender, young age, previous good health, antecedent febrile illness, CSF pleocytosis, very long-lasting SE, extensive negative workup and usually catastrophic outcome. Our patient presented first time ever with RSE, and a cause for same could not be ascertained despite extensive work up, thus qualifying to be labelled NORSE. Despite an initial good responsiveness of SE to thiopentone, the drug had to be withheld due to the unique problem of possibly life-threatening bradyarrythmia induced by thiopentone. Side effects and complications reported with thiopentone use include arterial hypotension, dyskalemia, respiratory complications, hepatic dysfunction and renal dysfunction.[5] Severe hypokalaemia and rebound hyperkalaemia resulting in cardiac asystole has been reported in a patient with traumatic subarachnoid haemorrhage following barbiturate coma therapy.[6] Our case describes a new finding—transient bradycardia and junctional escape rhythm unrelated to dyskalaemia as an early complication during thiopentone use. Among other AEDs, life-threatening arrhythmia has been reported following intravenous phenytoin.[7] In experimental models, phenytoin has been demonstrated to act at cardiac sodium and calcium channels.[8] Experimental studies have also demonstrated that pentobarbital, a close analogue of thiopentone, acts at ventricular sodium channels. Whether thiopentone caused transient bradycardia by acting at one of these channels may be worth probing further. Drug-induced transient bradycardia has been reported previously. In a retrospective analysis of drug-induced bradycardia, 5 of 38 (13%) patients resumed taking the culprit medication after discharge from the hospital without recurrence of bradycardia.[9]

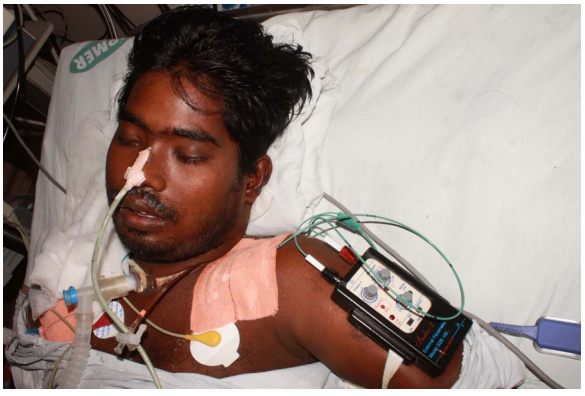

Figure 3 Temporary pacemaker inserted through left subclavian access while thiopentone infusion is continued.

Learning points

- The new onset refractory status epilepticus is a very difficult to treat condition.
- Bradyarrythmia, unrelated to electrolyte disturbance, could be an early complication of intravenous thiopentone sodium use.
- Mechanism needs elucidation by further research.
- Novel successfully executed therapeutic strategy of continuing thiopentone infusion with temporary pacemaker insertion to overcome the limitation imposed by this unexpected complication deserves attention.

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Competing interests None.

Patient consent Obtained.

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