CASE REPORT

DIAZEPAM IN SEVERE TETANUS TREATMENT

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Abstract. The causes of death in tetanus are muscle spasms and spasm of the larynx, which are caused by blocking the release of inhibitory neurotransmitters in the spinal synapses, causing the uncontrolled spread of impulses. Diazepam controls the spasms by blocking the polysynaptic reflexes, working peripherally, without depressing the cortical center and has no cardiovascular or endocrine effects. High dose diazepam had been used and proved to be a good muscle relaxant. Diazepam seems to work better with tetanus than pancuronium bromide, but both drugs need mechanical ventilation. In cases where the dose exceeds 240 mg per day in a child, a ventilator should be on hand, and if the dose required is more than 480 mg per day, other drugs should be considered. In three cases of severe tetanus presented here, the first two were managed by diazepam and pancuronium bromide and the last case by high dose diazepam only. In the first case, the dose of diazepam was up to 480 mg/day. By using high dose diazepam in severe tetanus, management of the clinical manifestations of autonomic nerve involvement and the weaning process become easier. Most complications of severe tetanus became more manageable.

Tetanus is an acute, spastic paralytic illness caused by tetanospasmin, a neurotoxin produced by *Clostridium tetani*. It is one of the very few diseases where the clinical manifestations are very characteristic (Krugman and Katz, 1992; Arnon, 2000). The clinical symptoms are not due to infection, but as a result from the action of tetanospasmin produced by the vegetative form of *Clostridium tetani* (Weinstein, 1992). Toxin blocks release of the inhibitory neurotransmitters glycine and GABA. With diminished inhibition, the resting firing rate of the alpha motor neuron increases, producing rigidity (Sommers, 1985; Daniel, 2000).

Death may result from asphyxia during generalized spasms accompanied by spasms of the larynx and respiratory muscles, or from secondary infection (particularly lung involvement), or from complications of treatment, especially respiratory and central nervous system depression (Gorbach,1990; Farrar, 2000).

Diazepam, a benzodiazepine and GABA agonist, is widely used. Diazepam has proved to be a very valuable drug, because it effectively controls spasms and hyper-tonicity without depressing the cortical center (Weinstein,1992). The dose required for controlling spasms is 0.1-0.3 mg/kg (Bleck, 1986; Dollery, 1991). Femi-Pearse (1966) began to use high dose diazepam in tetanus (in neonatal tetanus the dose was 40 mg/kg) and afterwards a wide range of doses were used. Most of the doses were relatively 'high' compared to the doses for ordinary seizures (Ismoedijanto *et al*, 1981; Okuonghae and Airede, 1992). In Dr Sutomo Hospital, Surabaya, diazepam is given according to the severity criteria developed by the Division of Pediatric Infectious Disease and Tropical Pediatrics. In cases where the usual dose fails, a high dose and a neuromuscular blocking agent should be used. A neuromuscular blocking agent together with mechanical ventilation should not be used except in situations in which control of seizures is very difficult or respiratory failure has occurred (Kaspan, 1994; Jerram, 1988).

The purpose of this paper is to present three

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cases of severe tetanus, treated with high dose diazepam, alone or in combination with pancuronium bromide.

Case 1

An 11 year-old boy was admitted to the Department of Child Health, Dr Soetomo Hospital on January 17, 2000 with a chief complaint of spasms. He had suffered from generalized spasms an hour before admission and the patient remained conscious. His arms and legs were rigid and he had difficulty opening his mouth beginning eleven hours before admission. He had a 'nail-puncture' wound a week before admission. Basic immunization was uncertain and no booster immunizations had been given.

Physical examination on admission revealed an alert boy with a body weight of 30 kg. Vital signs were within normal limits. There was trismus (less than 1 cm), risus sardonicus and neck stiffness with a board-like abdomen. On the sole of the left foot, there was a sign of a puncture wound without any swelling or tenderness. The neurological examination showed increased deep tendon reflexes, without any pathological reflexes. The laboratory examination on admission revealed: hemoglobin: 14.5 g/dl, leukocyte: 4,000/mm^3, thrombocyte count was normal, erythrocyte sedimentation rate (ESR) was 18/hour, with a differential count of: -/-/2/45/52/1.

The patient was put on an intravenous fluid drip and nothing was given by mouth. Procaine penicillin was administered intramuscularly twice a day. Tetanus antitoxin 5,000 units and diphtheria and tetanus toxoids (DT) 0.5 ml were given simultaneously at different sites. Wound debridement was only done by performing a cross incision, washed by using 3% H_2O_2 followed by 10% povidone iodine. Diazepam 192 mg/day (1.6 ml/hour) was given by syringe pump and the convulsions ceased, but reappeared again. The dose of diazepam was increased to 216 mg/day (1.8 ml/hour).

On the 3rd day of hospitalization, the child experienced more frequent convulsions and the dose was increased to 240 mg/day (2 ml/hour). Additional boluses of diazepam 10 mg were administered if spasms were more severe or more frequent, providing that it did not exceed 4 times within 24 hours. In spite of vigorous treatment, the condition worsened and the patient had to be referred to the intensive care unit. In the ICU, pancuronium bromide was given with a dose of 1 mg/hour in addition to the diazepam 240 mg/day. The patient was put on a ventilator and closely observed for spasms. The spasms became less frequent, but he suffered from hyperhydrosis and hyperpyrexia, which were managed successfully. Chloramphenicol was added for bronchopenumonia. As he became better the dose of diazepam was reduced to 1.2 ml/hour.

On the 8th day of hospitalization, the clinical condition worsened again as spontaneous spasms reappeared. We re-explored the wound and removed a piece of fish bone with soil surrounded by necrotic tissue along with pus in the sole of the left foot. All of these foreign bodies and the contaminated tissue were removed. The patient was readmitted to the ICU, with the dose of diazepam of 1 ml/hour. The spasms were lessened and on the 10th day of hospitalization the pancuronium bromide was stopped.

General spasms became more frequent, but as we believe that diazepam is beneficial, the dose of diazepam was increased hourly to 480 mg/day (4 ml/hour). Over the next three days spontaneous spasms did not recur and the frequency of triggered muscle spasms decreased rapidly. The diazepam was decreased gradually to 1 ml/hour. The dose was reduced slowly, then changed to oral and the ventilator was weaned on the 23th day of hospitalization. The clinical condition improved quickly and the patient was discharged on the 34th day, after receiving a second dose of DT.

Case 2

AR, a 10 year-old boy was admitted due to spasms and could not open his mouth. He suffered from general spasms, two hours before admission, but he remained conscious. His arms and legs became rigid and he had difficulty opening his mouth beginning two hours before admission. A piece of wood had punctured the sole of his right foot about eight days prior to admission. Basic immunization was uncertain, and he never had any booster immunizations.

Physical examination on admission revealed an alert boy with a body weight of 22 kg, with normal vital signs. There was trismus, risus sardonicus and neck stiffness. We found a puncture wound on the sole of the right foot with a swollen tender area. Neurological examination showed hyperactivity of the tendon reflexes and

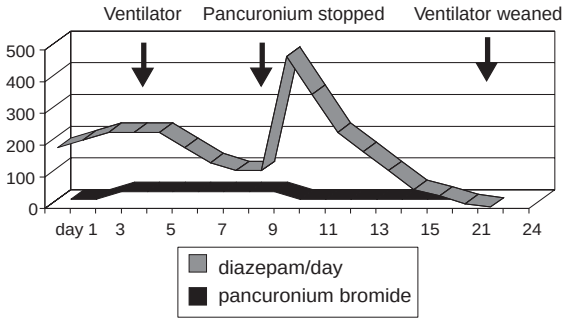

Fig 1–Daily doses of diazepam and pancuronium bromide in case 1.

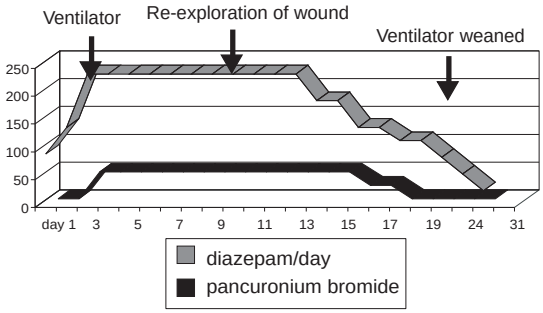

Fig 2–Daily doses of diazepam and pancuronium bromide in case 2.

an absence of pathological reflexes.

The laboratory examination on admission revealed; hemoglobin: 13 g/dl; leukocytes: 9,700/mm^3; thrombocytes: 352,000/mm^3; ESR: 52/hour, with a differential count of: -/-/2/64/34/-.

He was put on an intravenous fluid drip and procaine penicillin was administered twice daily. Tetanus antitoxin 5,000 units and diphtheria and tetanus toxoids (DT) 0.5 ml were given simultaneously at different sites. Wound debridement was done but there was no evidence of foreign bodies. Diazepam was started with a dose of 0.8 ml/hour by syringe pump, but on the second day of hospitalization, more spasms appeared and the dose of diazepam was increased to 1.2 ml/hour, but his condition worsened, then the diazepam was increased to 240 mg/day (2 ml/hour). Additional bolus injections of diazepam 10 mg were administered if spasms were severe or more frequent. The blood gas analysis revealed: pH: 7.02, P_aO_2: 52.9 mmHg, P_aCO_2: 74.2 mmHg, HCO_3: 19.0 mmHg and BE: -11.0, revealing impending respiratory failure.

The child was referred to the ICU for assisted ventilation, pancuronium bromide was given at 2 mg/hour in addition to diazepam 2 ml/hour. After a period of good response, on the 9th day of hospitalization the spasms persisted and a tracheotomy was done. We re-explored the wound and found a piece of wood (2.0x 0.5 x 0.1 cm) surrounded by necrotic tissue and pus in the sole of the right foot. The foreign body was removed and open wound care was done. An additional ATS 50,000 IU was given. Two days later the spasms ceased, but signs of rigidity were still present. Slowly the diazepam was reduced to 1.6 ml/hour and then changed to oral. Finally the pancuronium bromide was stopped on the 18th day of hospitalization.

On the 24th day of hospitalization the rigidity, which was now confined to the right leg, and the mechanical ventilation was stopped. Six days later, the dose of oral diazepam was 5 mg orally 6 times daily. And on the 44th day of hospitalization the patient was discharged in good condition.

Case 3

H, a 5 year-old girl was admitted to the Department of Child Health Dr Soetomo Hospital due to spasms. She suffered from spasms two hours before admission, but remained conscious. Rigidity and difficulty in opening her mouth were present seven hours before admission. She suffered from otorrhea of the left ear. Her basic immunizations were uncertain and no booster injections had been received.

Physical examination on admission revealed an alert girl with a body weight of 11.5 kg. There was no cyanosis or dyspnea. There was trismus, risus sardonicus, neck stiffness and pus caming from the left ear. The neurological examination showed hyperactive deep tendon reflexes and an absence of pathological reflexes.

The laboratory examination on admission revealed: hemoglobin: 12.3 g/dl; leukocytes: 8,300/mm^3; thrombocytes: 453,000; with a differential count of: -/-/1/61/37/1.

She was put on an intravenous fluid drip and nothing was given by mouth. Procaine penicillin was administered twice a day. Tetanus antitoxin 5,000 units and diphtheria and tetanus toxoids (DT) 0.5 ml were given intramuscularly at different sites. Diazepam 192 mg/day (1.6 ml/hour)

was given by syringe pump. The spasms lessened, but on the next day increased and the dose of diazepam was increased to 216 mg/day (1.8 ml/hour).

The spasms then became more frequent, and the dose was increased to 240 mg/day (2 ml/hour). Additional bolus injections of diazepam 10 mg were administered during severe attacks. In spite of vigorous treatment, the condition worsened and the patient was referred to the intensive care unit, where she was put on a ventilator, with the same dose of diazepam. On the 5th day of hospitalization, the child experienced more frequent spasms, and the dose of diazepam was increased to 360 mg/day (3 ml/hour). The condition then improved, there were no spontaneous spasm and 3 days later the dose was decreased to 2 ml/hour (240 mg/day). The dose was decreased slowly and on the 15th day, the diazepam was being given at 4-mg per hour intravenously and 4 mg orally 12 times daily. Two days later, the mechanical ventilation was stopped and the diazepam was gradually decreased to 4 mg orally 3 times daily.

On the 25th day of hospitalization the patient was discharged in good condition.

The management of tetanus requires the greatest medical and nursing skill. In the absence of either, tetanus is a highly fatal disease. The treatment of tetanus is focused on the elimination of the organism by wound debridement, antibiotics, neutralizations of free toxin, control of muscle spasms and supportive care (Krugman and Katz, 1992). All patients with generalized tetanus need a muscle relaxant. Ideal drugs for the treatment of tetanus should control decrease spasticity without impairing respirations, voluntary movements or conciousness (Jerram, 1988; Dolley, 1991). The most difficult part of management is the control of convulsions. Before the use of diazepam, the spasms caused bone fractures.

The clinical feature of tetanus have been classified into mild, moderate and severe forms. The Division of Infectious Disease and Tropical Pediatrics, Airlangga University has developed criteria to classify the severity of tetanus (Kaspan *et al*, 1994), related to the proposed dose of diazepam. The criteria are:

- Mild cases have an incubation period greater than ten days and a slow evolution of classical signs. Trismus may be present, but generalized spasms and triggered spasms are absent.

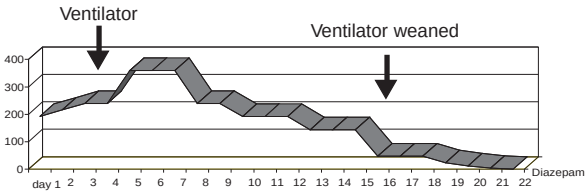

Fig 3–Daily doses of diazepam in case 3, without any pancuronium bromide.

- Moderate cases have an incubation period less than ten days with progressive development of symptoms over 3 to 6 days. Generalized spasms are late in onset, occur infrequently, and are not associated with respiratory difficulty. *Triggered spasms* occurred only by external stimuli.
- Severe cases of tetanus have a short incubation period, often less than three days, with a rapid evolution of sign and symptoms within 3 days of onset, strong rigidity and *spontaneous spasms* (Dolly, 1991).

For severe cases the dose of diazepam is started at 8 mg/kg/day (1.6 ml/hour), with a maximum of 240 mg/day (2.0 ml/hour). Moderate cases are started at 4 mg/kg/day (0.8 ml/hour). If the cilnical signs worsen quickly, the dose should be increased to 1.6 ml/hour or more. In mild cases, the dose is started at 4 mg/kg/day (0.8 ml/hour) and the dose changed to oral when possible.

Wound debridement should be undertaken in order to remove necrotic tissue, foreign bodies and anaerobic dead-spaces. In these patients wound debridement was done on admission but the foreign bodies were overlooked, forcing a re-exploration.

Procaine penicillin was given, since *Clostridium tetani* is usually sensitive to penicillin. Tetanus antitoxin can neutralize the newly produced toxin only when it is free and is only partially neutralizable when it is on the cell surface. Pinocytosis, internalizing the toxin, renders it nonneutralizable, thus fixation of toxin to nerves and its internalization result in an irreversible effect (Weinstein, 1992; Arnon,2000,). Once toxin is fixed in nervous tissue, antitoxin has no effect on it. Antibody produced actively by immunization can neutralize toxin better than the heterologous (horse) antitoxin. This is the reason for using both passive and active immunizations (Kaspan *et al*, 1994).

Tetanus treatment uses drugs which should decrease spasticity effectively without impairing respirations or conciousness. Diazepam is the muscle relaxant of choice because it is metabolized rapidly, has sedative properties, and effectively controls spasms and hypertonicity with less cortical depression (Gorbach, 1990). Many agents, alone and in combination, have been used including phenobarbitone, meprobamate, chlorpromazine, magnesium sulfate and diazepam (Cordova, 1969; Bleck, 1986).

Pancuronium bromide is a non-depolarizing neuromuscular blocking agent. The dose of pancuronium bromide required for neuromuscular blockage is extremely variable: the daily dose ranges between 100 and 1,100 μg/kg/day. This drug does not cross the blood brain barrier, therefore it has no effect on cerebral activity.

Diazepam, a benzodiazepine derivative, is an effective tranquilizing and sedative agent with potent muscle relaxant and anti-convulsive properties. It binds to receptors in various regions of the brain, such as the spinal cord, brain stem, cerebellum, limbic system and cerebral cortex. The binding of diazepam to the benzodiazepine receptor potentiates the inhibitory action of GABA upon the chloride channel, thereby enhancing GABA facilitated, inhibitory synaptic transmission.

The muscle relaxing activity of diazepam is about five times as great as that of phenobarbitone but its hypnotic action is only about one-sixth. Because the major clinical effect of tetanospasmin occurs at inhibitory synapses in the brainstem and spinal cord, therapy aims to restore inhibition at these levels. Of the variety of agents that share this mechanism of action, the benzodiazepines have been studied most thoroughly and appear to be the most effective (Bleck, 1986).

Table 1
Summary of clinical and laboratory examinations and treatment outcomes of the three cases.

	Case1	Case2	Case3
Identity	A/male/11yrs/30kg	AR/male/10yrs/22kg	H/female/5yrs/11.5kg
Main complaint	spasms	spasms	spasms
Incubation period	7 days	3 days	Uncertain
Period of onset	6 hours	2 hours	7 hours
Basic immunization	uncertain	uncertain	Uncertain
Port of entry	wound puncture	wound puncture	Ear
Severity	severe	severe	Severe
Clinical manifestations			
Consciousness	+	+	+
Rigidity	+	+	+
Triggered spasm	+	+	+
Spontaneous spasms	+	+	+
Complications			
Hyperpyrexia	+	-	-
Hyperhydrosis	+	+	-
Hypertension	-	+	+
Laboratory examinations			
Hemoglobin	14.5	13.0	12.3
Leucocytes count	4,000	9,700	8,300
ESR	18	52	?
Differential count	0/0/2/45/52/1	0/0/2/64/34/0	0/0/1/61/37/1
Treatment			
Antibiotics	Penproc + chloro	Penproc + chloro	Penproc
Antitoxin + DT	+	+	+
Wound debridement	2x	2x	Ear toilette
Diazepam	Max 480	Max240	Max 360
Pancuronium bromide	Max2	Max2	No
Ventilator	23 days	24 days	17 days
Discharge after	34 days	44 days	25 days

Diazepam is absorbed rapidly and completely after oral administration and peak plasma concentration is reached in 15-30 minutes in children. The recommended dose is 0.1-0.3 mg/kg body weight intravenously at intervals of 1-4 hours. For maximum benefit the dosage should be carefully adjusted to the individual patient (Dollery, 1991). The lethal dose of diazepam in man is not known. According Khoo *et al* (1978), once spontaneous spasms had ceased for at least 48 hours, the dose of diazepam may be reduced every third day by approximately 10% of the previous dose.

Herrero reviewed published and unpublished reports of about 300 patients with tetanus treated with diazepam in doses ranging from 30 mg to 400 mg daily, alone or in combination with sedatives or muscle relaxants. He concluded that, in addition to its muscle relaxant action, the sedative and antianxiety effects of diazepam and its tendency to induce amnesia are useful for eliminating the restlessness, excitement, hyperirritability and apprehension that are known to trigger tetanic seizures. When used concomitantly with barbiturates or other muscle relaxants, diazepam potentiated the effects of these drugs and reduced their required doses considerably (Cordova, 1969).

Cordova (1969) reported on three patients with severe tetanus who were treated with diazepam intravenously in doses of 0.5 to 25 mg/kg/day, which controlled spasms without complications.

Khoo *et al* (1978) used a combination of a continuous intravenous infusion of diazepam (20-40 mg/kg/day) and intragastric phenobarbitone to treat neonatal tetanus. Ismoedijanto *et al* (1981) used a continuous infusion of diazepam (40 mg/kgBW) in neonatal tetanus and a maximum of 200 mg/day in children, before the use of assissted ventilation.

Most authors noted that over sedation, respiratory depression, cardiovascular and autonomic side effects seemed less severe and frequent with diazepam than with therapeutically equivalent doses of barbiturates or other muscle relaxants (Christie, 1987; Dollery, 1991).

The tetanic spasms appeared to be controlled rapidly and smoothly by diazepam when administered without other sedatives or muscle relaxants. We feel that well controlled studies in large numbers of patients with severe tetanus given adequate doses of diazepam may furnish more definitive answers as to its effects.

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