Barbiturate Abstinence Syndrome

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The method of treatment of severe tetanus at our institution has been outlined previously 1,2 and includes in part the use of intravenous or intramuscular amobarbital. This report presents an example of a barbiturate abstinence syndrome occurring in a patient having severe tetanus who received approximately 2.4 g. of amobarbital per day for 25 days. Unfamiliarity with this syndrome delayed the diagnosis and the institution of specific therapy.

CASE REPORT

A 33 year old farmer's wife was admitted to the University of Minnesota Hospital on June 10, 1963, with a diagnosis of tetanus. Antibiotic therapy with penicillin was begun and the patient was sedated with intramuscular chlorpromazine (25 mg. q. 6 h.) and intravenous sodium amobarbital (100 mg. q. 2 h.). Seventeen days after injury and 5 days after the first symptom, the patient had a convulsion. A tracheostomy was performed, the patient was paralyzed with gallamine triethiodide, and sedated with chlorpromazine and amobarbital. An intermittent positive pressure respirator provided adequate alveolar ventilation.

For the next 17 days, the patient remained paralyzed with gallamine triethiodide (75 mg. q. 12 h.) and sedated with chlorpromazine (25 mg. q. 6 h.) and sodium amobarbital (150-200 mg. q. 2 h.). Gallamine triethiodide was then discontinued and the following day the chlorpromazine was stopped. At this time the patient was receiving an average daily dose of 3.6 g. of sodium amobarbital intravenously. On July 3, the route of administration of the amobarbital was changed from intravenous to oral. She received 2.3 g. on July 4, and 0.9 g. on July 5, via naso-gastric tube. The amobarbital was discontinued at 5:30 A.M., July 5, 1963.

The patient's vital signs on July 3 were: blood pressure 140/80 mm. of mercury, pulse rate 100, respiration 16 per minute, and a rectal temperature of 100.4°F. At this time she was sitting up and could tolerate 15 minutes without respiratory assistance. On July 4, at 2:30 A.M., her rectal temperature rose to 102°F and her blood pressure rose to 190/100. Her pulse rate increased to 140 and her respiratory rate increased to 26 breaths per minute. By 7:30 A.M. her vital signs had returned to their previous values.

On July 5, the patient was apprehensive and was unable to tolerate more than five minutes without respiratory assistance. At 9:30 P.M., her rectal temperature increased to 103.4°F, her blood pressure increased to 170/100, her pulse rate rose 20 beats per minute to 120 and her respiratory rate increased from 16 to 30 breaths per minute. These signs remained unchanged except for the blood pressure which fell to 140/90, despite symptomatic therapy, acetylsalicylic acid and mild hypothermia.

During the day of July 6, the patient became more agitated, felt weaker and was unable to breathe without respiratory assistance. She complained of blurred vision and nausea. Abdominal cramps became severe and she developed a loose watery diarrhea. At 8:00 P.M. her blood pressure rose to 220/120, her pulse rate increased to 140 beats per minute, her respiratory rate increased to 40 breaths per minute and her temperature rose to 103.2°F. Following 100 mg. amobarbital into her naso-gastric tube and 25 mg. of chlorpromazine intramuscularly her temperature decreased to 101°F and her blood pressure dropped to 125/100. Her pulse rate and respiratory rate remained unchanged. At this time urine and blood samples were taken to be cultured. A roentgenogram of the chest showed only a continuing improvement of a

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left lower lobe pneumonia which had been present since June 21. Urine samples were sterile and the blood cultures grew what were reported as "Gram-negative rods." These "Gram-negative rods" were subsequently identified as a skin contaminant, coccobacillus minae, and not *Pseudomonas aeruginosa* as was suspected.

At 11:15 P.M. the patient had a generalized grand mal convolution lasting 45 seconds with a 5-10 minute postconvulsive stuporous period. At this time 300 mg. of sodium amobarbital was given intravenously. Physical examination demonstrated the presence of generalized hyperreflexia, neck rigidity and normal retinal fundi. There were no localizing neurological signs. A blood culture taken at this time was subsequently reported as sterile and spinal fluid examined was also normal and sterile.

Laboratory examinations performed on venous blood indicated blood urea nitrogen of 13 mg./100 ml., bicarbonate of 25 mEq./liter, chloride of 100 mEq./liter, sodium of 138 mEq./liter, potassium of 4.4 mEq./liter, white blood cell count of 11,350 with 91 per cent neutrophils and hemoglobin of 10.3 g./100 ml. An arterial blood sample had a pH of 7.328, PaCO₂ was 38.7 mm. of mercury and oxygen saturation was 99.3 per cent.

On July 7, she received 1.7 g. of sodium amobarbital by nasogastric tube. Blood pressure was 120/70, pulse 100 beats per minute, rectal temperature 101° F. and her respiratory rate was 24 breaths per minute. On July 8,
her total dosage of sodium amobarbital was 300 mg. in three doses and seven hours after her last dose she once again had a mild grand mal convolution lasting 15–20 seconds.

On July 9, all antibiotics were stopped and she received 400 mg. of sodium amobarbital in divided doses by mouth. On July 10, she received her last two 100 mg. doses of sodium amobarbital by mouth.

Her recovery following this was rapid and uneventful and she was discharged from the hospital on July 23, 1963.

COMMENTS

In 1934, Gillespie stated that it was safe to acutely withdraw barbiturates from patients who had been chronically ingesting them. Meyer in 1939 described the seizures and “toxic hallucinatory psychosis” induced by the acute withdrawal of barbiturates from an addict. Kalinowsky in 1942 confirmed this withdrawal syndrome in seven patients who had been ingesting high doses (1.3 to 1.95 g. daily) of sodium barbital or sodium diethyl barbital and who were suddenly withdrawn from the drug. He summarized his findings by stating that “seizures from withdrawal of barbiturates do not occur after acute intoxication, appear seldom after short use of very large doses, as in narcosis treatment, but are frequent after withdrawal following chronic addiction.” He also concluded that the interval between withdrawal and convulsion or psychosis is fairly constant for each drug and that the convulsions seemed to be related to the time of total excretion of the drug.

In 1950 Isbell offered experimental evidence of a barbiturate withdrawal syndrome by inducing addition to quinalbarbital, pentobarbital, or amobarbital in five patients and then acutely withdrawing the drug. Convulsions occurred in four of the patients and four of the five became psychotic. Fraser, in 1953, reported a death due to the acute withdrawal of secobarbital.

The usual course of the barbiturate withdrawal syndrome is that for the first 12 to 16 hours after the withdrawal the patients appear to improve. Following this period increasing anxiety, apprehension, insomnia, weakness, tremulousness, nausea and vomiting appear. Deep reflexes are hyperactive and slight stimuli may cause exaggerated muscular responses. Abdominal cramps may become severe. Hyperpyrexia, tachypnea and hypertension ensue. After one to two days of insomnia and usually between the third and seventh day a psychosis characterized by confusion, disorientation, chiefly in place and time but not in person, delusions and visual and auditory hallucinations begin. These are worse at night and usually will subside without treatment within four to fourteen days.

Commonly between the second and fifth day of abstinence one or more grand mal seizures occur. Consciousness usually is gained within a few minutes and unlike idiopathic epilepsy prolonged stupor is uncommon although some confusion may be present for an hour or two.

The differential diagnosis in this patient was narrowed to a consideration of a brain abscess secondary to a septicemia, to systemic tetanus, to barbiturate withdrawal or to some other infective neurological disease.

The patient prior to the convulsion complained mainly of blurred vision and narrowing lateral fields of vision. A brain abscess or other infective neurological diseases were ruled out by appropriate examination.

Systemic tetanus was ruled out as the patient had only minimal muscle rigidity and no spasm after the withdrawal of the gallamine triethiodide. The wound was healing well by granulation and she had received more than adequate amounts of tetanus antitoxin.

A diagnosis of barbiturate withdrawal was made primarily by exclusion and secondarily by the results obtained from amobarbital administration. Interestingly the time of the onset of withdrawal symptoms appears to be related to the change in the route of administration from an intravenous one to an oral one. However, amobarbital was also rapidly reduced from a daily dose of 3.6 g. to 0.9 g. over a 36 hour period.

Because of unfamiliarity with the barbiturate withdrawal syndrome, proper and complete treatment was not carried out. The syndrome can be completely prevented by the gradual withdrawal of the barbiturate. This should be done in anyone who has received more than 0.4 g. of barbiturate per day. The daily dose should be decreased by no more than 0.1 g. per day and the dose should be
CORRESPONDENCE

Blood/Gas Partition Coefficient of Divinyl Ether

To the Editor.—Several current articles concerned with the uptake and distribution of anesthetic agents have made note that the blood/gas partition coefficient of divinyl ether was unknown. I have recently determined this value using the technique of Larson et al. In quadruplicate with pooled ACD bank blood (HCT 38-44). Aliquots of divinyl ether (0.2 ml) were injected into flasks of known volume containing blood. After agitation and equilibration with blood at 37° C. resulting gas concentrations were read on the halothane infrared analyzer. Values were calculated from the gas laws. A blood/gas partition coefficient of 2.8 ± 0.2 was determined.

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