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14. ABSTRACT
The present study established the toxicity of the nerve agent soman in the African green monkey (*Chlorocebus aethiops*). Seven male African green monkeys were implanted with telemetry devices to monitor electroencephalographic (EEG) activity. The up-down method of Dixon and Massey (1981) was used to estimate the LD_{50}. Soman was injected IM in the calf muscle. One subject was given 5.01 ug/kg soman; toxic signs (fasciculations, tremors, salivation) developed within 5 min with tonic-clonic motor convulsions and EEG seizure beginning shortly thereafter and persisted for ~1 hr. Toxic signs diminished over 6 hr and the animal recovered. Three animals were exposed to 6.31 ug/kg soman. Similar toxic signs developed; seizures and convulsions persisted 4-5 hr. Two animals recovered while the other animal developed spontaneous seizure/convulsions and failed to take nourishment. Three animals were exposed to 7.94 ug/kg soman. All developed severe seizures and motor convulsions accompanied by profuse salivation. Two animals died in <30 min, the third died ~5 hr after exposure. The 48-hr IM LD_{50} of soman was calculated to be 7.15 ug/kg. The African green monkey responds to soman exposure with the same progression of toxic signs and at similar dose levels as reported for rhesus monkeys.

15. SUBJECT TERMS
nerve agent, soman, anticonvulsant, seizures, Status epilepticus, African green monkey, rhesus monkey

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ABSTRACT

The rhesus monkey (*Macaca mulatta*) has been used for many years in the US as the main non-human primate model to examine mechanisms of nerve agent toxicity and to assess the effectiveness of medical countermeasures. Since the rhesus has become an increasingly difficult animal to obtain and care for, another model was needed. We have been studying the suitability of the African green monkey (*Chlorocebus aethiops*) as a replacement non-human primate model for the rhesus. The present study was designed to establish the toxicity of the nerve agent soman in this species.

Male African green monkeys, weighing 4.5-7.0 kg, were surgically implanted with telemetry devices to monitor electroencephalographic (EEG) and electrocardiogram (ECG) activity at least 2 months before the experiment. At least three baseline 24-hr records of EEG and ECG data were recorded in each animal before exposure. The up-down method of Dixon and Massey (1981) was used to estimate the unprotected LD_{50} for soman. The 48-hr intramuscular (IM) LD_{50} of soman has been reported to be 7.4 ug/kg in the rhesus monkey and 3.77 ug/kg in the cynomologus (*Macaca fascicularis*) monkey. The starting dose used in the present study was 5.01 ug/kg ($log_{10} = 0.70$) and was increased or decreased in 0.10 log_{10} increments depending upon the response of the previously tested animal. Soman (0.10 mg/ml, in saline) was injected IM in the calf muscle. The onset, duration and intensity of toxic signs were monitored and recorded.

Seven animals were exposed. The first subject was given 5.01 ug/kg soman; toxic signs (fasciculations, tremors, chewing, salivation) developed within 5 min with tonic-clonic motor convulsions and EEG seizure beginning shortly after that. Motor convulsions and EEG seizure persisted for ~1 hr and then spontaneously stopped. Fasciculations, tremor and salivation persisted and slowly diminished over the next 6 hr; the animal recovered and survived. Three animals were exposed to 6.31 ug/kg soman. Similar toxic signs developed in the same progression; EEG seizures, tonic-clonic motor convulsions and profuse salivation were the most prominent signs. All subjects had EEG seizures and convulsions that persisted for 4-5 hr; seizure activity slowly diminished and then stopped, and the animals regained consciousness several hours later. Two animals recovered without further incident. The other animal developed spontaneous seizure/convulsions and failed to take nourishment; his physical condition slowly deteriorated despite supplementary fluids, and he was euthanized 6 days after exposure for humane reasons. Three animals were exposed to 7.94 ug/kg soman. All developed severe EEG seizures and motor convulsions accompanied by profuse salivation. The condition of two animals deteriorated rapidly and they died in <30 min. The third animal died ~5 hr after exposure following >3 hr of seizure accompanied by declining heart rate and body temperature. The 48-hr IM LD_{50} of soman was calculated to be 7.15 ug/kg. The African green monkey responds to soman exposure with the same progression of toxic signs and at similar dose levels as reported for rhesus monkeys.

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INTRODUCTION

Non-human primates (NHP) are the animals phylogenetically closest to man. In the context of biomedical research, they have been considered to be the animal that physiologically most closely approximates how a drug or toxin would act in man (Miller, 1967; Dixon, 1976; Krasovskii, 1976). The rhesus monkey (*Macaca mulatta*) has traditionally served as the NHP research species of choice for the assessment of nerve agent toxicity and the assessment of the effectiveness of various medical countermeasures. The "choice" of the rhesus monkey, as can best be discerned, was probably a case of historical default. In the late 1940s, animal research into the toxicology of nerve agents and the development of medical countermeasures was first initiated in the US and various allied countries. At that time, rhesus monkeys were readily available and widely used for biomedical research in general. Research on the toxicology of the nerve agents and the assessment of medical countermeasures appears to have simply followed this trend (DeCandole et al., 1953; DeCandole and McPhail, 1957; Johnson et al., 1958; Lipp, 1968, 1973; Dirnhuber et al., 1979).

India, the major foreign source of rhesus monkeys, stopped exporting these animals for biomedical research purposes in the late 1970s. Subsequently, the increasing demand for these animals, coupled with limited domestic breeding sources, greatly decreased availability while substantially increasing cost. In addition, rhesus monkeys pose a serious health hazard to research and husbandry personnel due to the potential for transmission of *Cercopithecine herpesvirus 1* (termed B virus), which has exceptional virulence in humans (Artenstein et al., 1991; Davenport et al., 1994; Holmes et al., 1990). Protecting personnel from this virus requires additional personal protective equipment and special medical monitoring, all of which increase the overall husbandry and research costs of using these animals. For these reasons, there is a need to find an alternative monkey species to evaluate medical countermeasures against chemical warfare nerve agents. Two other NHP species have been reported to be used in this regard, the cynomologus monkey (*Macaca fascicularis*) (Lallement et al., 1997, 1998, 1999, 2000; von Bredow et al., 1991) and the common marmoset (*Callithrix jacchus*) (D'Mello and Scott, 1986; Wetherell and French, 1991; van Helden et al., 1992; Busker et al., 1996; Philippens et al., 2000). Both of these species have drawbacks. The cynomologus monkey also carries *Cercopithecine herpesvirus 1*, and thus poses a health risk and associated protective costs equivalent to the rhesus monkey. The marmoset monkey is a substantially smaller species (body weight 250-450 g), which limits the ability to take repeated blood samples and the availability of sampling sites.

The African green monkey (*Chlorocebus aethiops*) may be an ideal replacement for the rhesus monkey. African green monkeys are old world monkeys and grow to ~60% of the size of a rhesus. They are considerably less aggressive than rhesus and well-trained personnel can perform repeated blood sampling from superficial veins. African green monkeys are readily available from a variety of sources for ~30% of the price of a rhesus monkey, and most important, they do not carry *Cercopithecine herpesvirus 1*.

However, there are no previous toxicological or pharmacological research studies with nerve agents or any of the standard medical countermeasures using African green monkeys. Before an informed decision can be made as to the suitability of the African green monkey for future research, it is necessary to determine the comparability of data obtained with the African green monkey to historical data already available for the rhesus monkey. The present experiment was designed to determine the toxicity of the nerve agent soman in African green monkeys. The intramuscular (IM) dose of this agent that produced lethality in 50% of the animals (LD_{50}) was to be established along with a description of the time-course and severity of physiological signs of intoxication. An additional goal of this work was to use as few animals as possible for this determination.

METHODS

Subjects: Seven adult male African green monkeys, weighing 4.5-7.0 kg, served as subjects. The animals were individually housed in stainless steel cages equipped with a squeeze device for brief restraint. The animal quarters were under a 12-hr:12-hr light (0600-1800) – dark (1800-0600) cycle. Fresh water was freely available in the home cage. The animals were fed a diet of commercial primate chow supplemented with fresh fruit daily.

Surgery: Six of the seven animals were implanted with cortical EEG leads and a telemetry device (animal V5347 was not implanted). Animals were fasted overnight prior to surgery. The animal was anesthetized initially with ketamine (10 mg/kg, IM) and then intubated. Further anesthesia was maintained using Isoflorane (0.8-2% with nitrous oxide and oxygen in a 2:1 ratio). The animal was then placed in a Kopf stereotaxic frame and prepared for sterile surgery. Approximately 15 min before the first incision was made, the antibiotic cephazolin was administered 25 mg/kg, IV. A midline incision was made in the scalp, and burr holes were drilled in the skull over the frontal, central, temporal and occipital cortices bilaterally. Stainless steel screws were screwed into the holes. An incision was then made 5-8 cm below the left scapular region of the back, and a subcutaneous pouch created to accept the biopotential transmitter device (Models TL10M4-D70-EEEE, 4 channel or TL10M3-D70-EEE, 3 channel; Data Sciences International (DSI), St. Paul, MN). The leads from the transmitter were tunneled subcutaneously to the skull. The frontal and central screws on the left side served as one EEG channel, the temporal and occipital screws on the left side served as a second EEG channel, and the frontal and central screws on the right side served as a third EEG channel when a 4-channel transmitter was used (three animals). The frontal and central screws on the left side served as one EEG channel and the temporal and occipital screws on the right side served as a second EEG channel when the 3-channel transmitter was used (three animals). The leads were trimmed to length, a small (~0.5 cm) part of the silastic covering of the lead was removed and the bare lead wire was wrapped around the shaft of the screw; the screw was then turned into the skull anchoring the wire in place. The screw head and wire leads were covered with dental acrylic and the incisions closed using absorbable suture. Lead II ECG electrodes from the transmitter were tunneled subcutaneously and placed beneath the overlaying musculature using 2-0 Prolene to

anchor the wire electrode to the body wall. The negative lead was placed in the upper right chest quadrant near the heart base and the positive electrode was placed near the heart apex in the lower left chest quadrant. Muscle and fascia were closed in layers using simple interrupted pattern with absorbable suture; skin was closed with an intradermal continuous pattern using absorbable suture. All skin incisions were reinforced with tissue adhesive (Vetbond). Each animal received a systemic antibiotic (40,000 units/kg penicillin G benzithine, IM) and an analgesic (buprenorphine, 0.01 mg/kg, IM) postoperatively. Approximately 4-6 weeks passed between surgery and nerve agent exposure.

EEG Recording: EEG recordings were obtained by telemetry from freely moving animals in their home cages utilizing DSI Dataquest ART (version 2.3) software and displaying the signals on a computer monitor. At least three baseline recording sessions, 18 – 24 hr in duration, were obtained from each animal prior to nerve agent exposure. Recordings were obtained continuously during and for 48 hr after agent exposure. In surviving animals, 24-hr records were made on days 3, 10, 15, 30, 45, 60, 75 and 90 throughout the three-month survival time before euthanasia.

Nerve Agent Exposure: On the day of exposure, a blood sample was first obtained to serve as a pre-exposure acetylcholinesterase (AChE) and troponin baseline. The animal was then injected with the predetermined dose of soman (0.100 mg/ml in saline) in the calf muscle. Three soman doses were used in the experiment: 5.01 ug/kg (N=1), 6.31 ug/kg (N=3) and 7.94 ug/kg (N=3). EEG recording began within 1 min of injection and clinical observations were performed continually for at least 4 hr following exposure. Additional blood samples were obtained to measure AChE at 6 hr, 24 hr, 3, 10, 30, 60 and 90 days after exposure in survivors; the 6- and 24-hr blood samples were also assayed for troponin.

Cholinesterase Assay: Blood samples were placed in microfuge tubes containing 30 ul of EDTA to prevent clotting. Whole blood (~ 1 ml) was centrifuged (10 min, 14,000 rpm), and then 20 ul of packed red blood cells (RBC) were added to 980 ul of a 1% Triton X - saline solution. The RBCs were lysed by shaking and then flash frozen until assay. AChE determinations of RBCs were performed using a microtiter plate modification of the Ellman method (Hobson, 1988) that utilizes acetylthiocholine as a substrate.
Troponin Assay: Troponin-I was measured using a Troponin-I (2nd Generation) immunoassay kit (Tosho Medics, San Francisco, CA) and run on a Tosho AIA 600-II automated immunoassay instrument.

Experimental Design: An up-down design for small samples was used (Dixon and Massey, 1981). A dose of 5.01 ug/kg ($\log_{10} = 0.70$) was used as the starting dose. The rational for starting here was that this dose is roughly half way between the reported soman LD_{50} for rhesus monkeys (7.4 ug/kg, IM; Adams et al., 1976) and that of cynomologus monkeys (3.7 ug/kg, IM; Adams, 1990). Based on the toxic response of a particular test animal, alive vs. dead at 48 hr, the next soman dose was increased or decreased in a 0.1 $\log_{10}$ unit increment for the next test animal.

RESULTS

All soman doses elicited severe signs of nerve agent intoxication. Within minutes of soman injection, the animals developed chewing and/or facial automatisms. This was immediately followed by mild and intermittent tremor in the limbs, which shortly progressed to strong and continuous tremor in the whole body accompanied by facial grimacing. This phase was soon followed by uncoordinated thrashing movements that rapidly progressed to tonic-clonic convulsions, EEG seizures, loss of posture, and unresponsiveness to external stimuli. A profuse thick, ropy salivation developed and persisted throughout the period of seizure activity. EEG seizure activity and motor convulsions were prominent features of intoxication. Table 1 summarizes the times for seizure onset and their duration. Figure 1 provides an example of the EEG record of a seizure. There was a notable cycling of seizure/convulsive activity; it would primarily be characterized as clonic with intermittent intense episodes of tonic activity. After the first 15-30 min of seizure, there was notable waxing and waning of seizure/convulsive activity, with periods of 2-4 min quiescence in epileptiform EEG activity and convulsive movements between episodes of seizure/convulsive movements. This waxing and waning would become more prominent as the seizure duration grew longer (>1 hr).

Each challenge dose elicited a distinct progression and duration of toxic signs. The animal (V564) intoxicated with 5.01 ug/kg of soman had the longest latency for seizure onset and the seizures terminated after almost 1 hr. Shortly after termination of the seizures the animal slowly regained consciousness, although tremor, fasciculations and salivation were still evident for 4-8 hr as coordination and normal behavior returned. Within two days this animal appeared normal. Three animals (V471, V576, V584) were intoxicated with the 6.31 ug/kg dose of soman. These animals experienced seizure durations of 2.5-3.5 hr, and it was 2-8 hr after the seizure ended before evidence of consciousness (response to sound or touch, voluntary movement) returned. One animal (V471) initially appeared to recover, but displayed at least 3 spontaneous seizures (2- to 4-min duration) several days after the intoxication. This animal then failed to eat or drink and he was given subcutaneous fluids. Even with these measures his physical condition deteriorated to the point where a decision was made 6 days post-exposure to euthanize him for humane reasons. In contrast, the other two animals displayed uncoordinated behavior that slowly resolved over 1-3 days post-exposure, after which they appeared to fully recover. Three animals (V331, V361, V5342) were intoxicated with the 7.94 ug/kg dose of soman. After the initial progression of signs, two animals (V361, V5342) developed chaotic (Chynes-Stokes) respiratory efforts 10-15 min after exposure; cyanosis developed, seizure/convulsive activity rapidly declined, then periods of apnea developed accompanied by depressed heart rates. The animals died ~20 min after exposure. The other 7.94 ug/kg dose of soman animal (V331) displayed seizures for 1 hr 50 min. The seizure then spontaneously terminated; the animal continued to salivate profusely and over the next 4 hr there was a slow, steady decline in body temperature and heart rate until the animal died 6 hr after the exposure.

Blood (red blood cell) acetylcholinesterase was severely depressed (97-100%) relative to baseline values by soman exposure, with no real difference between doses. However, there was a notable recovery (6-20%; 94-80% of baseline) by 10 days after exposure.

Blood samples taken 6 hr after exposure for the three monkeys that received the 6.31 ug/kg dose of soman had elevated troponin levels (V584 = 0.64 ng/ml; V471 = 0.99 ng/ml; V576 = 6.55 ng/ml). Troponin levels >0.6 ng/ml are considered a clinically significant indicator of heart damage in humans, suggesting that these animals may have suffered cardiac damage.

Table 2 displays the dose sequence in which the animals were exposed, the response, and the detailed calculations recommended by Dixon and Massey (1981) used to estimate the IM LD_{50} of soman. Note that the variance (σ) in this calculation is assumed to be equivalent to the step-size (the increment between doses). Based on these calculations, the estimated 48-hr IM LD_{50} of soman = 7.15 ug/kg (6.28 – 8.13 ug/kg = $\pm$1 SEM).

DISCUSSION

The signs and speed of soman intoxication in African green monkeys were consistent with what has been described in the literature for the rhesus monkey, cynomologus monkey, and baboon (Adams et al., 1976; Adams, 1990; Anzueto et al., 1986). As Lipp (1968) had indicated, electrographic tonic-clonic seizures and motor convulsions were prominent aspects of the toxic symptomology of soman intoxication in all animals at the doses studied, although it must be emphasized that only one animal was exposed at the lowest test dose. The large increases in troponin seen at 6 hr after soman intoxication may be indicative of potential cardiac damage. Cardiac damage following soman exposure has been reported in rhesus and cynomologus monkeys as well as in baboons (Britt et al., 2000; Baze, 1993; Anzueto et al., 1986).

Table 3 displays reported LD_{50}s of soman in three large NHP species. The 48-hr IM LD_{50} of soman in African green monkeys in the present study was found to be 7.15 ug/kg. This dose is almost identical to LD_{50}s reported for soman in rhesus monkeys and baboons by other investigators (Adams et al., 1976; Olson et al., 1997; Anzueto et al., 1986). However, the 3.77 ug/kg 48-hr IM LD_{50} of soman in cynomologus monkeys reported by Adams (1990) appears to be excessively low based on the consistent LD_{50} values obtained in the other NHP species. Also, from the literature, it appears that subcutaneous injections of agent result in a higher LD_{50} value than do IM injections.

It should be noted that the LD_{50} value established in this study using the up-down method was accomplished with less than half the number of animals that were used in previous studies utilizing more traditional probit methods (Adams et al., 1976; Adams, 1990). Since the results obtained utilizing this design are comparable to and of the same level of precision as the traditional probit design, it is highly recommended that this up-down approach be utilized in all such future studies that involve NHP species.

Based on toxic response and LD_{50} value, the African green monkey appears to respond to the lethal effects of the nerve agent soman in an almost identical fashion to that of the rhesus monkey. Based on these data, this species appears to be an acceptable NHP model for assessing mechanisms of nerve agent toxicity as well as medical countermeasures.

Table 1
Onset of Tremors, Seizure Onset, Seizure Duration and Outcome

Subject	Soman Dose	Onset Tremor	Seizure Onset	Seizure Duration	Outcome
V564	5.01 ug/kg	7 min	17 min 29 sec	57 min	Lived 90 days
V471	6.31 ug/kg	3 min	6 min 38 sec	3 hr 23 min	Euthanized 6 days post-exposure
V576	6.31 ug/kg	6 min	14 min 11 sec	2 hr 54 min	Lived 90 days
V584	6.31 ug/kg	2 min	4 min 46 sec	2 hr 29 min	Lived 90 davs
V331	7.94 ug/kg	2 min	7 min 5 sec	1 hr 50 min	Died 6 hr
V361	7.94 ug/kg	2 min	2 min 21 sec	21 min	Died ~26 min
V5342	7.94 ug/kg	3 min	5 min 13 sec	18 min	Died ~25 min

Table 2

Summary of Animal Responses and LD_{50} Calculations for the Up-Down Method

Dose (µg/kg)	Log_{10} Dose	Response (animal tattoo)			
7.94	0.9		$X_{(V331)}$	$X_{(V361)}$	$X_{(V5342)}$
6.31	0.8	$0_{(V471)}$	$0_{(V576)}$	$0_{(V584)}$	
5.01	0.7	$0_{(V564)}$			

0 = 48 hr survival X = fatality

$LD_{50} = \chi_f + (K \times d)$ $LD_{50} = 0.9 + (-0.458 \times 0.1)$ $LD_{50} = 0.9 - 0.0458$ $LD_{50} = 0.8542_{(log10)}$ **LD_{50} = 7.15 ug/kg (6.28 – 8.13 ug/kg = ± 1 SEM)**	χ_f = last dose tested = 0.9 (log_{10}) K = Dixon & Massey table 19.2 = -0.458 d = interval between test doses = 0.1(log_{10}) N′ = total number of subjects tested = 7 N = sample size = 6 σ (variance) = d; SE = 0.56 σ

Table 3
Published Soman LD_{50} Values in Large Non-human Primate Species

Reference	Species	LD_{50}	Route	Diluent
Fukuyama & Askwich, 1963	rhesus	12.9 ug/kg*	SC	Not stated
Lipp, 1968	rhesus	9.5 ug/kg*	IM	Saline
Adams et al., 1976	rhesus	7.4 ug/kg (24-hr) 6.65 ug/kg (5-da)	IM	PEG - DH_2O
Dirnhuber et al., 1979	rhesus	12.3 ug/kg*	SC	Not stated
Olson et al., 1997	rhesus	7.3 ug/kg (48-hr)	IM	Saline
Adams, 1990	cynomolgus	3.77 ug/kg (24-hr)	IM	PEG - DH_2O
Anzueto et al., 1986	baboon	6.65 ug/kg (24 hr)	IV	Saline

*Survival times not stated.

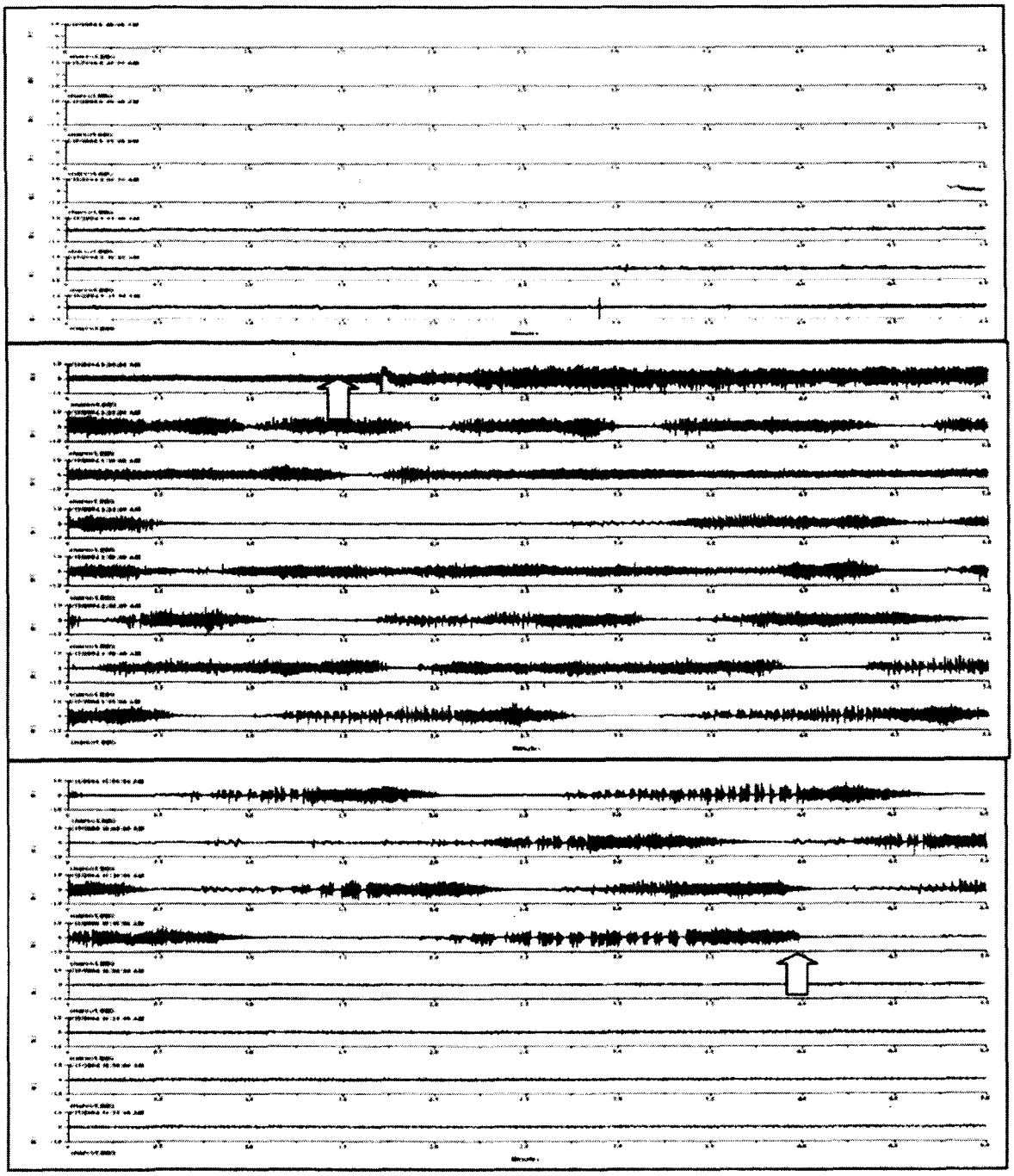

Figure 1. A continuous 95-min record of EEG following the administration of the 5.01 ug/kg dose of soman to subject V564. Each line is 5 min; the left frontal-central screws are the EEG leads recorded. Soman was given at 9:04 AM; the record starts one min later at 9:05 AM. Approximately 14 min after the start of the recording, there is a notable and sustained increase in EEG amplitude that culminates in seizure onset (top arrow) at 17.5 min after injection. The seizure continues uninterrupted at very high amplitudes for almost 5 min and then shifts into periods of waxing and waning of different durations for the next 52 min, where, at the end of a burst of rapid high amplitude spiking, the seizure abruptly ends (bottom arrow) and does not reoccur for the rest of the 24-hr record. Shortly (~10 min) after seizure termination the animal behaviorally demonstrated signs of alertness.

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