Laboratory Investigations

Brainstem auditory evoked potentials during procaine toxicity in dogs

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Although the toxic effect of local anaesthetics on the activity of cerebral cortex has been extensively studied, little is known about their toxic effect on brainstem. Accordingly, the influence of procaine on brainstem auditory evoked potentials (BAEPs) and on the electroencephalogram (EEG) was observed in 15 dogs. After the administration of procaine ($15 \text{ mg} \cdot \text{kg}^{-1}$, iv), the amplitudes of wave I (1.88 ± 0.56 vs $2.06 \pm 0.61 \mu\text{V}$, mean $\pm$ SD) and wave II (1.91 ± 0.41 vs $2.06 \pm 0.46 \mu\text{V}$) in BAEPs increased ($P < 0.05$), while the amplitudes of wave III (0.97 ± 0.27 vs $0.81 \pm 0.24 \mu\text{V}$), wave IV (1.15 ± 0.43 vs $0.85 \pm 0.29 \mu\text{V}$) and wave V (1.04 ± 0.46 vs $0.92 \pm 0.41 \mu\text{V}$) were decreased ($P < 0.05$), and both the I–III inter-peak latency (1.57 ± 0.04 vs $1.70 \pm 0.07 \text{ msec}$) and III–V inter-peak latency (2.15 ± 0.09 vs $2.35 \pm 0.12 \text{ msec}$) were prolonged ($P < 0.01$). The EEG changed from an awake pattern to seizure activity. These results suggest that the electrical activity of the brainstem auditory pathway is suppressed even when the cerebral cortex is in an excitatory state at the convulsive stage of procaine toxicity.

Les anesthésiques locaux ont des effets toxiques bien définis sur l'activité cérébrale corticale, mais leurs effets sur le tronc

cérébral sont moins bien connus. La présente étude faite chez 15 chiens évalue les effets de la procaine sur l'électroencéphalogramme (EEG) et sur les potentiels évoqués auditifs (PEA) au niveau du tronc cérébral. L'administration intraveineuse de procaine ($15 \text{ mg} \cdot \text{kg}^{-1}$) cause une augmentation des ondes I et II des PEA, de $1,88 \pm 0,56$ à $2,06 \pm 0,61 \mu\text{V}$ et de $1,91 \pm 0,41$ à $2,06 \pm 0,46 \mu\text{V}$ respectivement (moyenne $\pm$ écart-type $P < 0,05$), et une diminution des ondes III, IV et V de $0,97 \pm 0,27$ à $0,81 \pm 0,24 \mu\text{V}$, de $1,15 \pm 0,43$ à $0,86 \pm 0,29 \mu\text{V}$ et de $1,04 \pm 0,46$ à $0,92 \pm 0,41 \mu\text{V}$ respectivement ($P < 0,05$). La procaine prolonge la latence entre les pics I et III de $1,57 \pm 0,04$ à $1,70 \pm 0,07 \text{ msec}$ ($P < 0,01$) et entre les pics III et V de $2,15 \pm 0,09$ à $2,35 \pm 0,12 \text{ msec}$ ($P < 0,01$). Après injection de la procaine, le tracé d'EEG présente une activité de type épileptique comparativement à un tracé d'éveil avant l'injection du médicament. Ces résultats suggèrent qu'au moment où les effets toxiques de la procaine causent une excitation de type convulsif au niveau du cortex cérébral, l'activité au niveau du tronc cérébral est supprimée.

Key words

ANAESTHETICS, LOCAL: procaine;
MONITORING: electroencephalography, evoked potentials;
TOXICITY: local anaesthetics.

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Since the introduction of local anaesthetics into clinical practice, their systemic effect (toxic effect) has been a potential problem for the anaesthetist during regional anaesthesia.¹ In the main, toxicity occurs when the injection is made accidentally into a blood vessel. Manifestations of central nervous system (CNS) toxicity include numbness of the tongue, nervousness, light-headedness and visual and auditory disturbances. The higher blood levels can result in tremors and convulsions, and finally progress to global CNS depression.^{1–4} Although the toxic effect of local anaesthetics on the activity of the cerebral cortex has been extensively studied and is well known,^{5–8} the effect on the brainstem has not been clearly elucidated. The present study was designed to study the toxic effect of procaine on brainstem electrical activi-

ty by observing brainstem auditory evoked potentials (BAEPs).

Methods

After approval from the Animal Care Committee of the University, 15 mongrel dogs of either sex weighing 8–14 kg were studied. Ketamine ($20 \text{ mg} \cdot \text{kg}^{-1}$, *im*) and atropine (0.5 mg , *im*) were used to induce anaesthesia. After tracheal intubation, animals were paralyzed with pancuronium ($1.0 \text{ mg} \cdot \text{hr}^{-1}$) given by infusion and the lungs were ventilated mechanically using halothane (0.5–1.5%) in 60% nitrous oxide in oxygen. The ventilation was adjusted to maintain arterial carbon dioxide tension (PaCO_2) between 35 and 45 mmHg. A femoral artery catheter was inserted to monitor arterial pressure and to sample blood, and a thermal dilution catheter (Swan-Ganz, American Edwards Laboratory, U.S.A.) was inserted via femoral vein to administer drugs and fluid (lactated Ringer's solution, $7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$). The lower oesophageal temperature was monitored (43TA, Yellow Springs Instrument Co., Ohio, U.S.A.) and kept at about 38°C by regulating an infrared infant warmer and electrical blanket. Acid-base balance was corrected with sodium bicarbonate.

The BAEPs were observed from the right ear with the following method: click signals (alternate phasing) were presented mono-aurally with a 16 cm long tube (internal diameter: 2.5 mm) which was inserted into the external auditory meatus and fixed, at an intensity of 80 dB HL in 0.1 msec duration, and at a rate of 12.1 Hz. The BAEPs were recorded from a subcutaneous needle electrode at the skull vertex using an electrode at the mastoid process as reference. Electrode impedance was restricted to $<10 \text{ k}\Omega$ s (usually 4–6 k Ω s). A sweep time of 10 msec and a filter band pass of 300–1500 Hz were used. One thousand responses were averaged per trial and at least two trials were recorded and superimposed in order to define their reproducibility. The data were stored on magnetic disc for further analysis. The wave I to wave III inter-peak latency (I–III IPL) and the wave III to wave V inter-peak latency (III–V IPL) in BAEPs were measured. The length of a vertical line drawn from the positive peak to the cross point with the line between adjacent negative peaks in BAEPs was calculated as the amplitude. A BAEP computer (C4 Console, Nicolet instrument corporation, U.S.A.) was used for the observation.

The electroencephalogram (EEG) was continuously monitored from frontal-parietal leads (needle electrode) bilaterally⁹ (Multichannel Record RM-600, Nippon Kouden, Japan). The cardiac output was measured by thermo-dilution.

About 20 min after the ventilation gas was switched

TABLE The amplitude (μV) changes in brainstem auditory evoked potentials

	Pre-procaine	Post-procaine	P
Wave I	1.88 ± 0.56	2.06 ± 0.61	$P < 0.01$
Wave II	1.91 ± 0.41	2.06 ± 0.46	$P < 0.05$
Wave III	0.97 ± 0.27	0.81 ± 0.24	$P < 0.01$
Wave IV	1.15 ± 0.43	0.85 ± 0.29	$P < 0.01$
Wave V	1.04 ± 0.46	0.92 ± 0.41	$P < 0.05$

Mean $\pm$ SD.

to 0.2% halothane in oxygen and the end-expired halothane concentration reached $0.2\% \pm 0.05\%$, procaine $15 \text{ mg} \cdot \text{kg}^{-1}$ was injected intravenously over ten minutes. (As procaine has some anaesthesia effect^{10,11} no other anaesthetics or sedatives were given.) The BAEPs were recorded just before and after the injection.

Data are reported as mean values $\pm$ SD and were analyzed by paired Student t test. A $P < 0.05$ was considered to be statistically significant.

Results

The mean weight of the dogs was $11.1 \pm 1.7 \text{ kg}$ and the mean dose of procaine was $166.5 \pm 25.5 \text{ mg}$. About four hours elapsed between the anaesthesia induction and procaine administration. The lower oesophageal temperature (38.0 ± 0.1 vs $38.0 \pm 0.2^\circ \text{C}$, NS) and the base excess (-1.3 ± 1.1 vs $-1.3 \pm 1.8 \text{ mEq} \cdot \text{L}^{-1}$, NS) did not change after the injection of procaine.

The mean arterial pressure increased from $111 \pm 10 \text{ mmHg}$ to $122 \pm 16 \text{ mmHg}$ ($P < 0.05$), the heart rate decreased from $151 \pm 17 \text{ bpm}$ to $137 \pm 15 \text{ bpm}$ ($P < 0.05$), but the cardiac output did not change (1.88 ± 0.58 vs $1.78 \pm 0.55 \text{ L} \cdot \text{min}^{-1}$, NS).

In BAEPs, five waves could be clearly identified in all dogs. The wave I and wave II amplitudes in BAEPs increased ($P < 0.05$), while the amplitudes of wave III, IV and V decreased ($P < 0.05$) (Table), and both the I–III IPL (1.57 ± 0.04 vs $1.70 \pm 0.07 \text{ msec}$) and III–V IPL (2.15 ± 0.09 vs $2.35 \pm 0.12 \text{ msec}$) were prolonged after the administration of procaine ($P < 0.01$) (Figure 1). Figure 2 is an example of these changes. In one dog, waves III and IV became a III/IV complex, which has no clinical importance⁵ but was excluded from the amplitude and IPL statistical comparison. The EEG changed from an awake pattern to seizure activity (Figure 3).

Discussion

Procaine resulted in increases in the amplitudes of BAEP early components (wave I and wave II), decreases in the amplitudes of BAEP late components (wave III, wave IV and wave V), and prolongations in BAEP I–III IPL and

FIGURE 1 The mean (SD) I-III and III-V IPL (inter-peak latency) in brainstem auditory evoked potentials (BAEPs) after administration of $15 \text{ mg} \cdot \text{kg}^{-1}$ procaine. * $P < 0.01$ compared with pre-procaine value.

FIGURE 2 An example of brainstem auditory evoked potential composite changes after administration of $15 \text{ mg} \cdot \text{kg}^{-1}$ procaine.

III-V IPL. The EEG changed from an awake pattern to seizure activity.

Auditory evoked potential is a recently developed computer averaging technique which reflects the conduction of the brainstem auditory pathway.¹² Its high reproducibility makes it possible to be used more widely in the study of CNS electrical activity.¹³⁻¹⁷ During the present study, factors which may affect the BAEPs were well controlled. The animal's temperature was kept constant, the BAEP electrodes were fixed, and the stimulating conditions were not changed. The BAEPs were recorded after nitrous oxide was discontinued, and the halothane concentration had reached 0.2%.¹² The effect

FIGURE 3 The electroencephalogram changed from awake wave to seizure activity after administration of $15 \text{ mg} \cdot \text{kg}^{-1}$ procaine.

of ketamine on the BAEPs remains controversial^{18,19} but this possibility should not be considered in the present study. The BAEPs changed very rapidly (ten minutes), about four hours after the ketamine was injected *im*, whereas the effect of intramuscular administration of ketamine lasts only about 30 to 60 min.²⁰

Procaine is an ester-type drug. As with many other local anaesthetics, given intravenously in large doses or rapidly absorbed from peripheral sites, severe results including convulsions, coma, respiratory depression and cardiovascular collapse may occur. The aetiology of the convulsive stage is presumed to be depression of inhibitory neurons, creating an excitatory state akin to temporal lobe epilepsy.^{1,8} Electrical seizure activity can be observed on the EEG.^{7,8} At higher local anaesthetic concentrations, all neurons are affected, leading to global CNS depression and an isoelectric EEG.¹ In the present study, in order to prevent movement of electrodes and/or displacement of the stimulating tube, the animals were paralyzed and their lungs were ventilated mechanically. No convulsion or respiratory depression could be observed. Although the procaine concentration in the blood was not measured, the electrical seizure activity on EEG, which correlates with the severity of the clinical manifestation,⁸ suggests that the cerebral cortex was in an excitatory state and that procaine reached levels at the convulsive stage of local anaesthetic toxicity.^{1,7,8}

It is said the I-III IPL in BAEPs is a measure of conduction in the more caudal segment of the brainstem auditory pathway, and III-V IPL is a measure of conduction in the more rostral pontine and midbrain portions of the pathway.¹² Although the meaning of the increases in amplitudes of BAEP early components (wave I and wave II) which reflect the electrical activities of auditory

nerve and cochlear nuclei,¹² is unclear, the amplitudes of wave III, IV and V which reflect higher nervous activity of brainstem¹² decreased. Similar to the effects of some general anaesthetics,²¹⁻²⁴ the I-III and III-V IPLs were prolonged. Both the decreases in amplitudes of wave III, IV and V and the IPL prolongations suggest that the activity of the brainstem auditory pathway is suppressed.¹²

Clinically, effects of local anaesthetics on the brainstem (brainstem anaesthesia) may be observed after retrobulbar blockade or after interscalene brachial plexus block.^{25,26} The symptoms include the decline of hearing ability. This suggests that the activity of the auditory pathway in brainstem anaesthesia is depressed, and that electrical activity suppression of the auditory pathway in the present study may be the direct effect of procaine toxicity on the brainstem. The response of the EEG and the BAEPs in the present study was different which may reflect different responses in cortical and brainstem regions. Also, the possibility that the difference was caused by different procaine concentrations in these two regions should not be excluded.

In summary, our results demonstrated that the electrical activity of brainstem auditory pathway is suppressed even when the cerebral cortex is in the excitatory state during the convulsive stage of procaine toxicity.

References

- 1 Voulgaropoulos DS, Johnson MD, Covino BG. Local anesthetic toxicity. *Seminars in Anesthesia* 1990; 9: 8-15.
- 2 Finucane BT. Regional anaesthesia: complications and techniques. *Can J Anaesth* 1991; 38: R3-10.
- 3 Reynolds F. Adverse effects of local anaesthetics. *Br J Anaesth* 1987; 59: 78-95.
- 4 Scott DB. Toxicity caused by local anaesthetic drugs. *Br J Anaesth* 1981; 53: 553-4.
- 5 Dunne NM, Kox WJ. Neurological complications following the use of continuous extradural analgesia with bupivacaine. *Br J Anaesth* 1991; 66: 617-9.
- 6 Savarese JJ, Covino BG. Systemic effects of local anaesthetics (local anesthetic toxicity). In: Miller RD (Ed.). *Anesthesia*, 2nd ed., New York: Churchill Livingstone Inc., 1986: 1003-5.
- 7 Munson ES, Paul WL, Embro WJ. Central-nervous-system toxicity of local anaesthetics mixtures in monkeys. *Anesthesiology* 1977; 46: 179-83.
- 8 Usubiaga JE, Wikinski J, Ferrero R, Usubiaga LE, Wikinski R. Local anesthetic-induced convulsions in man - an electroencephalographic study. *Anesth Analg* 1966; 45: 611-20.
- 9 Herin RA, Purinton PT, Fletcher TF. Electroencephalography in the unanesthetized dog. *Am J Vet Res* 1968; 29: 329-36.
- 10 Gu ZH. The effects of intravenously given procaine on the enflurane MAC. *Chinese Journal of Anesthesiology* 1985; 5: 264-6.
- 11 Xie R. Survey of the clinical use of intravenous procaine anesthesia. *Chinese Journal of Surgery* 1985; 23: 610-2.
- 12 Stockard JV, Stockard JE, Sharbrough FW. Brainstem auditory evoked potentials in neurology: methodology, interpretation, and clinical application. In: Aminoff MJ (Ed.). *Electrodiagnosis in Clinical Neurology*, 2nd ed., New York: Churchill Livingstone Inc., 1986: 467-503.
- 13 Facco E, Munari M, Liviero MG, et al. Serial recordings of auditory brainstem response in severe head injury: relationship between test timing and prognostic power. *Intensive Care Med* 1989; 14: 422-8.
- 14 Newlon PG. Utility of multimodality evoked potentials in cerebral injury. *Neurol Clin* 1985; 3: 675-86.
- 15 Lutschg J, Pfenninger J, Ludin HP, et al. Brainstem auditory evoked potentials and early somatosensory evoked potentials in neurointensively treated comatose children. *Am J Dis Child* 1983; 137: 421-6.
- 16 Dong WK, Bledsoe SW, Eng DY, et al. Profound arterial hypotension in dogs: brain electrical activity and organ integrity. *Anesthesiology* 1987; 58: 61-71.
- 17 Thornton C, Barrowcleiffe MP, Konieczko KM, et al. The auditory evoked response as an indicator of awareness. *Br J Anaesth* 1989; 63: 113-5.
- 18 Cohen MS, Britt RH. Effects of sodium pentobarbital, ketamine, halothane, and chloralose on brainstem auditory evoked response. *Anesth Analg* 1982; 61: 338-43.
- 19 Church MW, Gritzke R. Effects of ketamine anesthesia on the rat brain-stem auditory evoked potentials as a function of dose and stimulus intensity. *Electroencephalogr Clin Neurophysiol* 1987; 67: 570-83.
- 20 Kaka JS, Hayton WL. Pharmacokinetics of ketamine and two metabolites in the dog. *J Pharmacokinet Biopharm* 1980; 8: 193-202.
- 21 Thornton C, Konieczko KM, Knight AB, et al. Effect of propofol on the auditory evoked response and oesophageal contractility. *Br J Anaesth* 1989; 63: 411-7.
- 22 Chassard D, Joubaud A, Colson A, et al. Auditory evoked potentials during propofol anaesthesia in man. *Br J Anaesth* 1989; 62: 522-6.
- 23 Drummond JC, Todd MM, Sang H. The effect of high dose sodium thiopental on brain stem auditory and median nerve somatosensory evoked responses in humans. *Anesthesiology* 1985; 63: 249-54.
- 24 Sebel PS, Ingram DA, Flynn PJ, Rutherford CF, Rogers H. Evoked potentials during isoflurane anaesthesia. *Br J Anaesth* 1986; 58: 580-5.
- 25 Hamilton RC. Brain stem anesthesia following retrobulbar blockade. *Anesthesiology* 1985; 63: 688-90.
- 26 Durrani Z, Winnie AP. Brainstem toxicity with reversible locked-in syndrome after intrascapular brachial plexus block. *Anesth Analg* 1991; 72: 249-52.