The effect of high-dose fentanyl on human median nerve somatosensory-evoked responses

Armin Schubert MD, John C. Drummond MD FRCPC, David O. Peterson MD, Lawrence J. Saidman MD

Median nerve somatosensory evoked responses (MnSSERs) were recorded in nine neurologically normal adult cardiac patients before and during the administration of high-dose fentanyl. MnSSERs were recorded prior to induction and at t = 20 min and t = 45 min postinduction. Fentanyl was administered as a slow bolus (53.2 ± 9.1 $\mu g \cdot kg^{-1}$), followed by a continuous infusion at 10– 20 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (total dose 63.6 ± 10.1 $\mu g \cdot kg^{-1}$).

All MnSSER waveform components remained recordable and easily identifiable during anaesthesia. The effect of fentanyl was more pronounced on cortical waveform components, leaving subcortical components largely unaffected. There was a significant increase in the latency of the cortical MnSSER at t = 20 min, e.g., for the initial negative cortical wave, N_1, the latency was 21.18 ± 1.55 ms preinduction versus 22.18 ± 1.42 ms at t = 20 min. There was also a significant decrease in the amplitude of the cortical response at t = 20 min, i.e., 2.04 ± 1.30 μV preinduction versus 1.31 ± 0.74 μV at t = 20 min. However, the degree of change was quite variable (range = 0–65 per cent). No further changes occurred at t = 45 min.

The authors conclude that MnSSERs can be consistently and reliably monitored during high-dose fentanyl anaesthesia. However, fentanyl produces modest but significant changes in the MnSSER which should be taken into account lest they be misinterpreted as neurologic injury in evolution.

Key words

ANAESTHETICS, INTRAVENOUS: fentanyl; BRAIN: evoked potentials, evoked responses; MONITORING: evoked potentials, evoked responses.

From the Uniformed Services University of The Health Sciences, Naval Hospital, Bethesda, MD (AS) and the University of California, San Diego.

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Address correspondence to: Dr. John C. Drummond, Neuroanesthesia Research, M-029, La Jolla, CA 92093.

High-dose fentanyl anaesthesia is frequently employed for patients undergoing major neurologic and cardiovascular surgery. Sensory evoked response (SER) monitoring may be relevant during certain of these procedures. Accurate interpretation of SER changes requires a knowledge of the effect of the anaesthetic in use on the evoked response waveform, since anaesthetics can produce SER changes mimicking an injury pattern. We sought to define the effect of fentanyl in doses exceeding 30 $\mu g \cdot kg^{-1}$ on the human median nerve somatosensory evoked response (MnSSER).

Methods

This study was approved by the Committee on Investigations Involving Human Subjects of the University of California, San Diego. Nine neurologically normal adult subjects (mean age 66 ± 11 years) scheduled for valve replacement or coronary artery bypass grafting were studied. Each gave informed consent. At the time of the study, the majority of the patients were taking one or more chronic medications for the treatment of their cardiovascular disease or other medical conditions, none of which are known to affect SERs.

The night before surgery, patients received either lorazepam 2 mg or flurazepam 30 mg PO. On the day of surgery, premedication consisted of diazepam 0.1–0.2 mg PO and morphine 0.08–0.15 mg IM (three patients received, in addition, scopolamine 0.2–0.4 mg IM) 30–60 min prior to transfer to the operating suite. Radial, pulmonary artery, and intravenous catheters were inserted under local anaesthesia. The latter was placed in the forearm contralateral to the extremity to be stimulated for MnSSER recording.

MnSSERs were recorded using a Pathfinder II Electrodiagnostic Monitor (Nicolet Biomedical, Madison WI 53711). The stimulation sites over the median nerve at the wrist were identified with a block electrode stimulator (interelectrode distance = 3 cm). Adhesive electrodes were applied and the stimuli, which consisted of 200 constant current impulses of 100 μsec duration, were

delivered at a rate of 3.1/sec. Stimulus intensity was adjusted to motor threshold + 50 per cent.

MnSSER waveforms were obtained simultaneously on three amplifier channels from recording electrodes (gold disk type, Grass Instruments) placed over the ipsilateral brachial plexus (Erb's point – Channel 1), the spinous process of the second cervical vertebra (C2S – Channel 2) and the contralateral sensory cortex (C_3' or C_4' – Channel 3), each referenced to FPz (International 10–20 system). The ground electrode was located over the mastoid process. Electrode impedances were maintained at less than 3 kOhms. The acquired signals were amplified 120,000 times (corresponding to a Pathfinder sensitivity setting of 50 μV). Bandpass filters were set at 30 and 250 Hz* and a timebase of 40 msec following the stimulus was analyzed. All recordings were obtained in duplicate and compared for reproducibility. They were stored on magnetic disk for subsequent measurement of latency and amplitude using electronic cursors.

An example of a typical waveform acquired from an awake subject and analyzed in this manner is shown in Figure 1. The nominal negativities N9, N14 and N20 are referred to in this communication as Erb's (Point), C2S, and N1 respectively, and the positive deflection immediately following N_1 as P_1. Amplitude measurements were made from each negativity to the succeeding positive waveform peak. To lessen the impact of patient height on cortical latencies, the central conduction time (CCT) was calculated as the C2S-N_1 interwave latency.

Control MnSSERs were obtained 10–15 min prior to induction. Anaesthesia was induced with fentanyl (53.2 ± 9.1 $\mu g \cdot kg^{-1}$, range 36–71 $\mu g \cdot kg^{-1}$), administered as a slow intravenous bolus over 10–20 min. The inspired gas was 100 per cent oxygen throughout and a pancuronium/metocurine combination was administered when responsiveness was lost. Following the bolus dose, a continuous infusion of fentanyl (10–20 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) was maintained throughout the study period. MnSSER recordings were repeated 20 min (t = 20) and 45 min (t = 45) after the induction dose of fentanyl. The t = 20 recording was always made prior to incision, while the t = 45 recording occurred immediately before sternotomy. The cumulative fentanyl dose was 55.0 ± 8.6 $\mu g \cdot kg^{-1}$ at t = 20 min and 63.6 ± 10.1 $\mu g \cdot kg^{-1}$ at t = 45 min.

*We routinely employ a relatively low high-band pass filter in order to reduce the high frequency noise common in the operating room. This has proven compatible with easy elicitation of waveforms (Figure 1), although average latencies are somewhat increased relative to those obtained with a higher high-band pass setting.

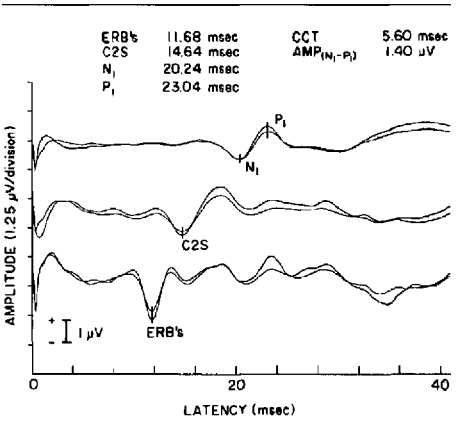

FIGURE 1 Control MnSSER recorded from an awake subject.

Arterial blood gas analysis including determination of haematocrit (Hct) was performed preinduction and approximately 30 min postinduction (t = 30). Ventilation was adjusted to maintain a normal end-tidal CO_2 (mass spectrometry). Mean arterial pressure (MAP) and core temperature (CT) obtained from the pulmonary artery catheter were recorded continuously and noted at the time of MnSSER acquisition. To prevent local cooling, the stimulated extremity was wrapped. A heater-humidifier, fluid warmer and heating blanket were employed to maintain CT.

Statistical analysis

The MnSSER latency and amplitude measurements obtained before (control) and after fentanyl (t = 20 and t = 45) were subjected to a repeated measures analysis of variance. If a significant change in a given measurement was detected, pairwise comparisons were performed using the Bonferroni t-test with appropriate corrections for multiple comparisons.

Results

The PaO_2, $PaCO_2$, $ETCO_2$, haematocrit, MAP and CT data appear in Table 1. There were no differences in $PaCO_2$, $ETCO_2$ and MAP throughout the study. The PaO_2 was always in excess of 60 mmHg preinduction and in excess of 140 mmHg at t = 30. CT was unchanged at t = 20 but significantly lower at t = 45 (35.4 ± 0.6°C) when compared with control (36.0 ± 0.5°C).

In two patients, the Erb's point potential could not be identified on the preinduction waveforms recorded from

TABLE I Physiologic patient data (mean ± SD)

	Control (preinduction)	*Postinduction*		
		t = 20	*t = 30*	*t = 45*
Haematocrit (%)	42.4 ± 5.2	—	35.1 ± 4.4*	—
PaO_2 (mmHg)	>60	—	>140	—
$PaCO_2$ (mmHg)	42.4 ± 6.4	—	40.1 ± 4.8	—
$ETCO_2$ (mmHg)	—	27.6 ± 2.5	—	27.6 ± 2.7
MAP (mmHg)	84.2 ± 17.3	78.8 ± 14.7	—	79.9 ± 15.8
CT† (°C)	36.02 ± 0.47	35.57 ± 0.70	—	35.37 ± 0.61*

*Significantly different ($p < 0.05$) vs control.
†CT = core temperature.

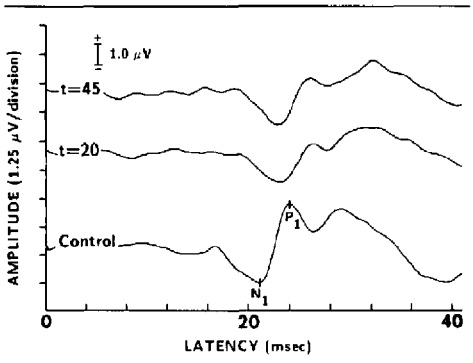

FIGURE 2 Cortical MnSSER preinduction, and during (t = 20 and t = 45 min) high-dose fentanyl anaesthesia.

the brachial plexus. This was probably the result of muscle/motion artifact, as the familiar negativity of the Erb's point potential returned after induction of anaesthesia and muscle relaxation. The data presented for Erb's Point were derived from only those seven patients in whom a complete data set was obtained. The remainder of MnSSER recordings were reproducible and allowed identification of all waveform components without difficulty. An example of the cortical MnSSERs recorded during the study period is provided in Figure 2. The latency and amplitude data at control, t = 20 and t = 45 are presented in Tables II and III, respectively. At both t = 20 and t = 45 the C2S, N_1 and P_1 latencies were significantly increased and the N_1-P_1 amplitude was significantly decreased from control. CCT was significantly prolonged only at t = 45. The latency and amplitude of each MnSSER component was never significantly different at t = 45 when compared to t = 20. The latency increase (Table II) and amplitude reduction (Table III) were more pronounced in the cortical (N_1, P_1) waveforms than in the subcortical components (C2S, Erb's).

TABLE II Latency (msec) after high dose fentanyl (mean ± SD) (n = 9†)

	Control	*t = 20*	*t = 45*
Erb's	11.89 ± 1.18	12.21 ± 1.69	12.22 ± 1.70
C2S	15.52 ± 1.65	15.96 ± 1.52*	16.02 ± 1.54*
CCT	5.59 ± 0.94	6.23 ± 0.99	6.48 ± 1.18*
N_1	21.18 ± 1.42	22.18 ± 1.55*	22.50 ± 1.52*
P_1	24.68 ± 2.81	26.32 ± 2.46*	26.36 ± 2.50*

*Significantly different ($p < 0.05$) vs control.
†n = 7 for Erb's point.

Discussion

Our results indicate that large doses of fentanyl result in changes in the amplitude and latency of human MnSSERs and that the effects on the cortical response are the most pronounced. While there are no prior studies which systematically examine the effect of high-dose fentanyl on somatosensory evoked responses (SSER's), several investigators have studied the effects of lower doses. Velasco *et al.*[1] recorded MnSSERs in 55 awake adults 30 min after administration of either placebo or fentanyl at various doses (2.5, 5.0 and 10.0 $\mu g \cdot kg^{-1}$). They found no change in the latency of a positive deflection at approxi-

TABLE III Amplitude (μV) after high-dose fentanyl (mean ± SD; n = 9†)

	Control	*T = 20*	*t = 45*
Erb's	1.31 ± 0.59	1.06 ± 0.83	1.17 ± 0.85
C2S	1.52 ± 0.60	1.37 ± 0.60	1.25 ± 0.54
N_1-P_1	2.04 ± 1.30	1.31 ± 0.74*	1.33 ± 0.74*

*Significantly different ($p < 0.05$) vs control.
†n = 7 for Erb's point.

mately 23 msec, yet observed a significant reduction in amplitude of a later waveform component (P150). It is difficult to compare these observations with our results, since Velasco *et al.* do not report numerical amplitude and latency values at different doses of fentanyl. Grundy *et al.*[2] also studied the effect of low-dose fentanyl (2.1 $\mu g \cdot kg^{-1}$) on the SSER's (posterior tibial nerve stimulation) of awake patients. They found an inconsistent increase in the amplitude of the primary specific complex but did not specify which component wave was analyzed or whether latency was affected.

Pathak *et al.*[3] investigated the effect of fentanyl and morphine on posterior tibial SSERs in 32 patients (ages 12–45 years) undergoing scoliosis surgery. Recordings were obtained preinduction and at 30 and 150 min after induction with thiopental 3 $mg \cdot kg^{-1}$ and fentanyl 2.5 $\mu g \cdot kg^{-1}$. Following induction, fentanyl was administered either by intermittent bolus or by continuous infusion to a total operative dose of 0.1 and 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. These authors observed a dose-related increase in latency of the waveforms of the primary specific complex with a variable decrease in amplitude. Although they do not report the cumulative fentanyl doses for the 30 and 150 min postinduction recordings, it appears that the maximum dose of fentanyl at 150 min could not have exceeded 15 $\mu g \cdot kg^{-1}$. Finally, in dogs given 25 $\mu g \cdot kg^{-1}$ fentanyl, McPherson *et al.*[4] found the MnSSER latency of a waveform component at approximately 23 msec to be prolonged by 1.2 msec. Despite differences in stimulus and recording parameters, subject population and narcotic dose, our results conform to the general trend observed by these previous investigators.[3,4]

It is recognized that the number of patients studied in the present report is small and that the standard deviations of our data are substantial. However, the study was designed such that each patient served as his or her own control. The magnitude of the observed standard deviations at control, t = 20 and t = 45 is therefore primarily a result of variability between patients, not between groups at different times of observation. The fact that statistical significance was achieved in spite of the large standard deviations, was occasioned by the homogeneous response of the evoked response parameters studied (e.g., cortical latencies increased in every single patient with high dose fentanyl). Because of this uniformity of response, little additional information could be gained by increasing the sample size.

In addition to anaesthetic agents, a number of factors can influence SSERs.[5,6] These include changes in MAP, haemotocrit, oxygenation and $PaCO_2$. However, none of these is likely to have contributed to the observed MnSSER alterations in the present study (see Table II). Changes in peripheral nerve conduction can also affect SSERs.[7] Although internal jugular vein cannulation was performed between the control and t = 20 MnSSER recordings, the cannulation was performed preinduction and no patient complained of paresthesiae or had postoperative neurologic impairment of the upper extremity. In addition, all MnSSER recordings were completed prior to sternotomy. It is thus unlikely that brachial plexus injury either from cannulation of the internal jugular vein or from sternal retraction could have affected our results.

Our somewhat restrictive high frequency filtering may have resulted in slightly longer average latencies than would be observed with the bandpass filters commonly employed in neurophysiology laboratories. This should not, of itself, detract from the validity of our results, since patients acted as their own controls. However, the absolute values of our evoked response parameters are not strictly comparable with those obtained at other clinical laboratories.

Decreased body temperature can affect SSERs by increasing latency and decreasing amplitude.[8,9] While it is possible that the small decrease in CT at t = 45 might have contributed to the observed MnSSER changes, a major temperature-related effect is unlikely for several reasons. First, the significant MnSSER changes had already occurred at t = 20 when CT was statistically unchanged from control. Second, no further changes in the MnSSER were evident after t = 20 despite the fact that CT had decreased when compared to control. Even if temperature had affected our results, it could have done so only in a minor way. Lam *et al.*[9] observed no statistically significant change in human cortical MnSSER latency and amplitude with mild hypothermia. Those authors did, however, observe a trend towards an increase in latency and a decrease in amplitude. Specifically, an average decrease in nasopharyngeal temperature of 1.3° C caused an increase in cortical latency of 0.4 msec and a decrease in cortical amplitude of 23 per cent. Extrapolation from the data by Lam *et al.* indicates that the magnitude of any possible temperature effect on our data would be of the order of only 0.2 msec for latency and ten per cent for amplitude.

With the exception of CCT, which showed a trend toward prolongation at t = 20, but did not reach statistical significance until t = 45, no further significant MnSSER changes occurred after t = 20 despite the continued administration of fentanyl. This observation may reflect the maintainance of relatively constant end organ fentanyl levels as a result of the bolus plus infusion protocol. An alternate explanation may be that the influence of rising fentanyl concentration was balanced by an arousal effect caused by surgical stimulation.

The degree to which intraoperative SSERs may change and still be consistent with postoperative neurologic integrity is not well defined. While the persistent loss of the SER waveform has been widely reported to predict the occurrence of a postoperative neurologic deficit[10–12] the significance of various degrees of subtotal loss of the waveform is less certain. However, a reduction in amplitude by 50 per cent and a prolongation in latency by ten per cent has been arbitrarily employed by some[11,13] to define a "significant" intraoperative SER change. If these criteria are employed, then high-dose fentanyl may occasionally produce changes that might be suggestive of neurologic injury. While sustained latency changes in excess of ten per cent were not seen at Erb's point, C2S or N_1 in any patient, cortical amplitude reduction was in excess of 50 per cent at both 20 and 45 minutes in two of the nine patients. These changes are modest by comparison with the substantial changes in MnSSER's produced by deep levels (e.g., 1.5 MAC) of anaesthesia achieved with halothane, enflurane or isoflurane.[14]

In conclusion, our results indicate that MnSSERs can be consistently and reliably recorded during high-dose fentanyl anaesthesia in neurologically normal subjects. However, interpretation of evolving MnSSER trends during clinical monitoring should take into account the changes produced by this anaesthetic agent lest they be misconstrued as an evolving neurologic injury.

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Résumé

Les réponses du potentiel évoqué somatosensoriel du nerf médian (MnSSERs) ont été enregistrées chez neuf patients adultes cardiaques neurologiquement normaux, avant et pendant l'administration de fentanyl à haute dose. Les MnSSERs ont été enregistrées avant l'induction au t = 20 minutes et au t = 45 minutes post induction. Le fentanyl a été administré en bolus lentement (53.2 ± 9.1 $\mu g \cdot kg^{-1}$), suivi d'une perfusion continue de 10– 20 $\mu g \cdot kg^{-1} \cdot heure^{-1}$ (dose totale 63.6 ± 10.1 $\mu g \cdot kg^{-1}$).

Tous les composants des tracés MnSSER pouvaient être enregistrés et identifiés facilement lors de l'anesthésie. L'effet du fentanyl était plus prononcé sur les composantes corticales des tracés laissant les composantes sous corticales en général non affectées. Il y avait une augmentation significative dans la latence du MnSSER cortical à t = 20 minutes, par exemple, pour l'onde corticale négative initiale, N_1, la latence était de 21.18 ± 1.55 ms avant l'induction versus 22.18 ± 1.42 ms à t = 20 minutes. Il y avait aussi une diminution significative de l'amplitude de la réponse corticale à t = 20 minutes, i.e., 2.04 ± 1.30 μV avant l'induction versus 1.31 ± 0.74 μV at t = 20 minutes. Cependant le degré de changement était assez variable (écart = 0 − 62 pour cent). Aucun autre changement n'est survenu à t = 45 minutes.

Les auteurs concluent que les MnSSERs peuvent être surveillés régulièrement et avec confiance lors d'une anesthésie au fentanyl à haute dose. Cependant le fentanyl produit des changements minimes mais significatifs dans le MnSSER qui doivent être pris en considération afin de ne pas les interpréter comme étant des lésions neurologiques en évolution.