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Cigarette smoking does not affect thiopentone pharmacodynamic or pharmacokinetic behaviour

Purpose: Smoking affects the pharmacodynamic and pharmacokinetic behaviour of several drugs. In smokers, induction of anaesthesia is often stormy. In this study we have determined whether cigarette smoking affected thiopentone pharmacodynamic or pharmacokinetic behaviour during induction of anaesthesia.

Methods: Fifteen smokers and 15 non-smokers, scheduled for elective surgery, were studied. Heart rate, invasive arterial pressures and middle latency auditory evoked potentials were recorded awake and during thiopentone induction (9 mg·kg⁻¹ lean body mass), before and after tracheal intubation. Blood was sampled up to 24 hr after induction to measure thiopentone plasma concentrations and to calculate pharmacokinetic parameters.

Results: Anaesthesia was adequate in all patients, although haemodynamic intubation response was not blunted. Latencies or amplitudes of middle latency auditory evoked potentials (MLAEP) did not differ between the groups. The postintubation latencies of Nb waves were 48.9 ± 8.1 msec (mean $\pm$ SD) in smokers and 48.1 ± 8.5 msec in non-smokers. Pharmacokinetic data showed no differences between smokers and non-smokers. Clearance of thiopentone was 2.9 ± 1.1 ml·min⁻¹·kg⁻¹ in smokers and 3.3 ± 1.0 ml·min⁻¹·kg⁻¹ in non-smokers and elimination half life of thiopentone was 12.5 ± 6.3 hr in smokers and 10.7 ± 3.1 hr in non-smokers, respectively. The haemodynamic response after the induction dose of thiopentone and after tracheal intubation were similar in smokers and non-smokers. Mean postintubation systolic arterial pressures were 192 ± 35 vs 189 ± 20 mmHg and mean postintubation heart rates were 103 ± 12 vs 102 ± 17 beat per minute (bpm) in smokers and non-smokers, respectively.

Conclusion: We conclude, that cigarette smoking does not affect the pharmacodynamic or pharmacokinetic behaviour of thiopentone.

Objectif : Le tabagisme influence le comportement pharmacodynamique et pharmacocinétique de plusieurs produits. Chez le fumeur, l'induction de l'anesthésie est souvent mouvementée. Cette étude visait à déterminer si la cigarette affectait le comportement pharmacodynamique et pharmacocinétique du thiopental pendant l'induction de l'anesthésie.

Méthodes : Quinze fumeurs et 15 non fumeurs programmés pour une intervention non urgente participaient à l'étude. La fréquence cardiaque, la pression artérielle sanglante et les potentiels auditifs de latence moyenne ont été enregistrés à l'état vigile et pendant l'induction de l'anesthésie au thiopental (9 mg·kg⁻¹ de poids maigre), avant et après l'intubation de la trachée. Du sang a été prélevé dans les 24 h suivant l'induction pour le dosage plasmatique du thiopental et le calcul des paramètres pharmacocinétiques.

Résultats : Tous les patients ont reçu une anesthésie satisfaisante mais sans qu'il y ait eu abolition de la réponse hémodynamique à l'intubation. Les latences ou amplitudes des potentiels évoqués auditifs de latence moyenne (MLAEP) ne différaient pas entre les groupes. Après l'intubation, la latence des ondes Nb était $48,9 \pm 8,1$ ms (moyenne $\pm$ ÉT) chez le fumeurs et $48,1 \pm 8,5$ ms chez les non fumeurs. La clairance du thiopental était de $2,9 \pm 1,1$ ml·min⁻¹·kg⁻¹ chez les fumeurs et de $3,3 \pm 1,0$ ml·min⁻¹·kg⁻¹ chez les non fumeurs ; la demi-vie d'élimination du thiopental était de $12,5 \pm 6,3$ chez les fumeurs et de $10,7 \pm 3,1$ chez les non fumeurs. La réponse hémodynamique après la dose d'induction de thiopental et après l'intubation ne différait pas entre les deux groupes. Après l'intubation, la pression artérielle systolique respective des fumeurs et des non fumeurs était 192 ± 53 vs 189 ± 20 mmHg et la fréquence cardiaque moyenne respective postintubation était 103 ± 12 vs 102 ± 17 bpm.

Conclusion : La cigarette n'a pas d'influence sur le comportement pharmacodynamique et pharmacocinétique du thiopental.

CIGARETTE smoking alters the pharmaco-
dynamic[1,2] or pharmacokinetic[1-4] behaviour
of many drugs. For example, smokers receiv-
ing benzodiazepines appear to be more resis-
tant to their sedative effects than are non-smokers. This
reduced drowsiness may be due to diminished end-
organ responsiveness in smokers.[5] Smoking is known to
induce drug metabolising enzymes, especially in the
liver.[1-4] Thus, the metabolism of hepatically eliminated
drugs, like thiopentone, might be modified by cigarette
smoking. Smoking is a predisposing factor to coughing,
mucous hypersecretion, breath holding and laryn-
gospasm during anaesthesia.[6] It has been suggested, that
these symptoms are due to increased airway reflex sensi-
tivity,[7] but they may also be caused by inadequate levels
of anaesthesia in smokers.

Altered drug response cannot always be explained by
variable pharmacokinetic behaviour. Thiopentone is a
commonly used intravenous hypnotic with a wide inter-
individual variation in dose requirement.[8,9] The effect
of tobacco smoking on the pharmacodynamics of
thiopentone is not clear. Objective measures have not
been used to compare the pharmacodynamic potency
of thiopentone between smoking and non-smoking
patients. Therefore, we studied the pharmacodynamic
and pharmacokinetic behaviour of thiopentone in
smokers and non-smokers in a clinical setting. We
hypothesised that smokers were more resistant to the
effects of thiopentone than non-smokers.

Methods

Based on our own unpublished data, the mean Nb wave
latency of auditory evoked potential after thiopentone
induction and tracheal intubation is 49 msec, with stan-
dard deviation around 8.5 msec. It was calculated, that
15 patients were needed in each group to demonstrate
a 20% latency difference at a level of significance of
$P < 0.05$ and power of 85%. These 30 subjects would
have 85% power to show 16% difference in the clear-
ance of thiopentone.[10] We obtained institutional
approval and written informed consent to study 15
smokers and 15 non-smokers, all ASA I, scheduled for
elective general or urological surgery (Table I).
Smokers inhaled >15 cigarettes daily. Patients who were
receiving regular medication, had a body mass index[11]
>27, were >50-yr-old or who consumed >20 units
alcohol (one unit = a glass of wine, a bottle of beer or
one drink) per week were excluded from the study.

In all patients the radial artery was cannulated under
local anaesthesia for invasive blood pressure monitoring
and a large cubital vein was cannulated for intravenous
infusion. A Neuropack Four mini (Nihon Kohden Ltd;
Japan) evoked potential device was used for acoustic
stimulation and recording of evoked potentials. Clicks

TABLE 1   Demographic data (mean ± SD).

	Smokers	Non-smokers
n	15	15
Sex (M/F)	9/6	10/5
Age (yr)	37 ± 10	40 ± 10
Weight (kg)	72 ± 7	72 ± 11
Height (cm)	174 ± 7	173 ± 8
LBM (kg)	54.7 ± 5.1	53.8 ± 6.8
Thiopentone dose (mg)	507 ± 43	500 ± 62

of 85 dB above normal hearing level were presented to
the patients binaurally via headphones at a rate of 9.0
Hz. Recording electrodes were positioned at the fore-
head and at the right mastoid. Inter-electrode imped-
ances were maintained < 5.0 kΩ. In each recording, 500
clicks of 0.1 msec were averaged using 20–1000 Hz
bandpass, 8-bit resolution, A/D conversion time of 10
msec and epoch time of 100 msec. Artifacts were
detected automatically and rejected. The typical time
required to acquire a waveform was 60 sec. Latencies
and amplitudes were measured manually on the screen
of the evoked potential device. Vertical and horizontal
cursors were used. In amplitude measuring, Na-Pa dif-
ference, (i.e., Pa amplitude), as well as Pa-Nb difference
(Nb amplitude) were calculated. All latencies and
amplitudes were analysed blinded by one of the authors
(HT) (Figure 1).

Anaesthesia was induced with thiopentone
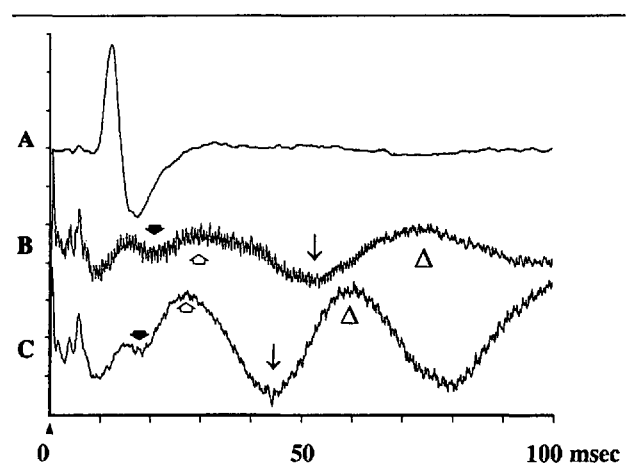9 mg·kg^{-1} lean body mass (LBM).[12] This is equal to

FIGURE 1   Auditory evoked potential registrations in one patient.
A = averaged response awake (amplitude 5 μV·div^{-1}). B = response
after thiopentone induction (0.62 μV·div^{-1}). C = response after
tracheal intubation (0.62 μV·div^{-1}). Binaural stimulus was presented
at 0, and each response was averaged up to 100 msec.

●, ○, ↓ and Δ indicate Na, Pa, Nb and Pb waveforms, respectively.

approximately 7 mg·kg⁻¹ body weight in normal person. Thiopentone was given at a rate of 10 mg·sec⁻¹. Vecuronium, 0.1 mg·kg⁻¹, was given to facilitate tracheal intubation. The lungs were ventilated with oxygen 100% and the trachea was intubated 2.5 min after the thiopentone injection. Arterial pressures, heart rate and middle latency auditory evoked potentials (MLAEP) were recorded awake, immediately following the thiopentone injection and three minutes after thiopentone. After this, anaesthesia was continued according to the clinical needs.

Arterial blood samples were drawn into EDTA tubes immediately before administration of thiopentone and 2, 5, 15, 30, 45 and 60 min and 2, 4 and 6 hr after thiopentone. After this, venous blood samples were drawn at 12 and 24 hr after administration of thiopentone. Plasma was separated within 60 min and stored at -40°C until thiopentone concentrations were determined by high-performance liquid chromatography.[13] The detection limit of the assay was 0.2 μg·ml⁻¹. The coefficient of variation at 3.1 μg·ml⁻¹ was 4.4% (n = 13) and at 35.9 μg·ml⁻¹ 5.2% (n = 13). All patients were interviewed 24 hr after anaesthesia for memories associated with events occurring during anaesthetic induction.

The individual plasma concentrations were fitted to the following multiexponential function with the aid of a microcomputer-based nonlinear regression programme using iteratively reweighted least squares with reciprocal squared prediction weighting[14]

$$C_p(t) = \sum_{i=1}^{n} A_i e^{-a_i t}$$

where Cp(t) is the plasma concentration of thiopentone at time t, A_i is a zero-time intercept, and a_i is a disposition rate constant. The goodness of the fit was determined by Akaike's information criterion[15] and by assessment of randomness of "scatter" of actual data points about the fitted function. The initial estimates were obtained using an iterative curve stripping technique.[16] The pharmacokinetic parameters, "fast"and "slow" half-lives (T ½,1 and T½,2), volume of central compartment (V_c), steady-state volume of distribution (V_{ss}) and clearance (CL) were calculated according to standard formulae.[17] A correction was made for the infusion time.[18]

Pharmacokinetic parameters were compared with Student's t test. Two way ANOVA for repeated measurements, followed by post-hoc t tests were used for the statistical testing of pharmacodynamic parameters. Factors in ANOVA were smoking status and time; tests were repeated in three levels: preinduction, preintubation and postintubation. $P < 0.05$ was considered to indicate statistically significant differences.

Results

Except for smoking, the social habits did not differ: alcohol, coffee and tea consumption were moderate and at the same level in both groups. The induction of anaesthesia was accomplished smoothly in all patients. No patient had SpO_2 <97% and no patient moved or coughed during laryngoscopy and intubation. Anaesthesia was adequate in all patients, without recall of intraoperative events.

Thiopentone caused increases in the latencies of auditory evoked waveforms Na, Pa and Nb, and decreases in the amplitudes of Pa and Nb waveforms in both groups, compared with the pre-induction values (Table II). After tracheal intubation the latencies of auditory evoked waveforms Na, Pa and Nb shortened again in both smokers and non-smokers, compared with the pre-intubation values (Table II). No differences were seen between the smokers and non-smokers.

The decay of the thiopentone plasma concentrations could be described adequately with a biexponential function in all cases (Figure 2). The pharmacokinetic

TABLE II Auditory evoked potential data.

		Preinduction	Preintubation	Postintubation
L-Na	S	16.4 ± 1.8	24.2 ± 6.5*	19.9 ± 3.5†
(msec)	NS	15.8 ± 1.9	25.7 ± 6.7*	21.8 ± 5.4
L-Pa	S	26.6 ± 5.2	41.1 ± 10.3*	33.7 ± 6.7†
(msec)	NS	26.6 ± 5.9	39.6 ± 10.1*	32.5 ± 6.7†
L-Nb	S	33.7 ± 5.4	59.2 ± 12.7*	48.9 ± 8.1†
(msec)	NS	34.5 ± 8.0	60.6 ± 13.1*	48.1 ± 8.5†
A-Pa	S	5.7 ± 4.3	1.0 ± 1.5*	0.8 ± 0.3
(μV)	NS	6.6 ± 4.7	0.5 ± 0.3*	0.8 ± 0.4†
A-Nb	S	1.5 ± 1.1	0.7 ± 1.1*	0.8 ± 0.4
(μV)	NS	1.5 ± 1.8	0.6 ± 0.3	0.8 ± 0.6

mean ± SD; S = smokers, NS = non-smokers; L-Na = latency of Na wave, L - Pa = latency of Pa wave, L-Nb = latency of Nb wave; A-Pa = voltage difference between Na and Pa waves, A-Nb = voltage difference between Pa and Nb waves; Significance from preinduction values: $P < 0.05$* within the groups; Significance from preintubation values: $P < 0.05$† within the groups.
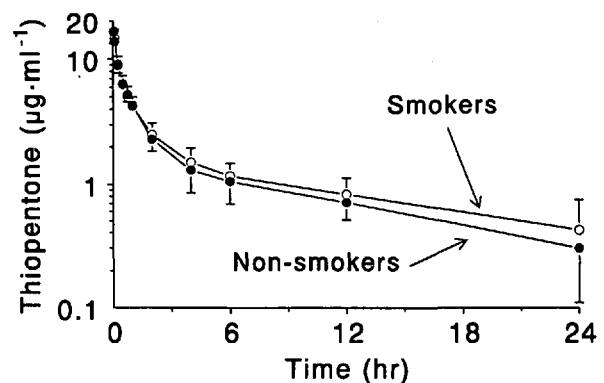

FIGURE 2 Concentrations (mean ± SD) of thiopentone in plasma after an induction dose of 9 mg·kg⁻¹ lean body mass to 15 smokers and 15 non-smokers undergoing general surgery.

TABLE III Pharmacokinetic data

	$V_c (l \cdot kg^{-1})$	$V_{ss} (l \cdot kg^{-1})$	CL $(ml \cdot min^{-1} \cdot kg^{-1})$	$T_{\frac{1}{2},1}$ (min)	$T_{\frac{1}{2},2}$ (hr)
Smokers	0.40 ± 0.09	2.2 ± 0.5	2.9 ± 1.1	23.9 ± 6.0	12.5 ± 6.3
Non-smokers	0.43 ± 0.10	2.2 ± 0.7	3.3 ± 1.0	25.9 ± 4.6	10.7 ± 3.1

(mean ± SD); V_c = volume of the central compartment, V_{ss} = volume of distribution at steady state, CL = clearance, $T_{\frac{1}{2},1}$ = "fast" half life and $T_{\frac{1}{2},2}$ = "slow" half-life.

TABLE IV Haemodynamic data

		Preinduction	Preintubation	Postintubation
SAP	S	155 ± 29	$127 \pm 24^*$	$192 \pm 35^+$
(mmHg)	NS	153 ± 21	$136 \pm 22^*$	$189 \pm 20^+$
HR	S	77 ± 13	$92 \pm 13^*$	$103 \pm 12^+$
(bpm)	NS	82 ± 19	88 ± 19	$102 \pm 17^+$

(mean ± SD); S = smokers, NS = non-smokers; SAP = systolic arterial pressure, HR = heart rate; Significance from preinduction values: $P < 0.05^*$ within the groups. Significance from preintubation values: $P < 0.05^+$ within the groups.

variables between smokers and non-smokers did not differ (Table III).

The haemodynamic intubation response was similar in both groups (Table IV). The systolic arterial pressures (SAP) increased from pre-intubation values in smokers and in non-smokers, but there was no difference between the groups. Heart rate increased in both groups, with no difference between groups.

Discussion

Cigarette smoking had no effect on the pharmacodynamic behaviour of thiopentone as quantified by auditory evoked potentials. Also the pharmacokinetics of thiopentone, as well as haemodynamic variables were similar in smokers and in non-smokers.

Thiopentone pharmacodynamics were evaluated using auditory evoked potentials, which have been validated as a reliable monitor of the adequacy of anaesthesia.[19] The middle latency auditory waves are thought to originate from the medial geniculate and primary auditory cortex.[20] Increases in the latencies of Pa and Nb waveforms indicate deepening unconsciousness.[19,21] The phenomenon is similar with most general anaesthetics.[19] Amplitudes of MLAEP's, on the other hand, seem to reflect patients' reaction to surgical stimulation. The amplitudes of Nb and Pb waveforms increase after start of surgery.[22] High dose fentanyl anaesthesia, providing excellent analgesia, blunts this response.[23] Increases in latency and decreases in amplitude of MLAEPs have also been noted following thiopentone induction.[19,24] In our study, too, the induction dose of thiopentone, 9 mg·kg⁻¹ LBM, caused a depression in cortical response as mea-

sured by MLAEP, while tracheal intubation caused an increase in responsiveness. Schwender et al. have shown that thiopentone induction produces an increase in the latencies and decrease in amplitudes of MLAEP for up to four minutes.[24] Those data correspond closely with ours up to two minutes after thiopentone administration. In our study the waves of MLAEP latencies decreased and amplitudes increased after tracheal intubation (three minutes after thiopentone administration) in both smokers and non-smokers, compared with pre-intubation values. This is, presumably, caused partly by the rapid change of the thiopentone concentration in the brain due to the drug redistribution and the lightening of anaesthesia produced by the stimulus of laryngoscopy and tracheal intubation.

After rapid intravenous administration of thiopentone the termination of its hypnotic effect is due to redistribution of the drug. Ultimately, thiopentone is eliminated hepatically. Derived parameters describing the distribution and elimination of thiopentone were similar in smokers and non-smokers. The values for V_{ss} varied from 1.1 to 3.1 l·kg⁻¹ and those of CL from 1.0 to 5.7 ml·min⁻¹·kg⁻¹. Both values were similar to those described previously.[10]

Several neurophysiological studies have shown depression in brain activity following the anaesthetic induction and an increase in brain activity after tracheal intubation.[24–28] The serum thiopentone concentration (Cp_{50}) that blunts the moving response in 50% of unparalysed patients for laryngoscopy was shown to be 50.7 μg·ml⁻¹, while the Cp_{50} for laryngoscopy and tracheal intubation was 78.8 μg·ml⁻¹.[25] In our study, the mean thiopentone concentration at the time of intubation was approximately 16 μg·ml⁻¹ both in smokers and in non-smokers. As the serum levels of thiopentone are not in equilibrium with brain after iv injection, relevant comparisons can hardly be performed. The haemodynamic responses to laryngoscopy and intubation were not blunted. The similar increase in SAP and heart rate in smokers and non-smokers shows that the immediate pharmacodynamic effect of thiopentone is unaffected by smoking. The mean Nb wave latencies after tracheal intubation were above 48 msec, indicating unconsciousness.[19] None of

the patients had any memory or any signs of conscious post-induction awareness.

We used a large dose of thiopentone (approx. 7 mg·kg⁻¹). This dose was chosen after pilot testing to avoid extremely high postintubation arterial pressures in patients not receiving opioids. We also wanted to ensure unconsciousness in unpremedicated patients by increasing the dose of thiopentone. Recently, Flaishon et al. showed that some patients can recover consciousness very rapidly after thiopentone, possibly even before intubation.[29] Due to our mode of administration of thiopentone, no recall occurred in our study. However, as the present data show, haemodynamic responses are poor measures of anaesthetic adequacy after thiopentone.

To our knowledge, this is the first study where auditory evoked potentials were used to measure the effect of smoking on thiopentone pharmacodynamics. In a study by Dundee et al.,[8] where the abolition of the eyelash reflex was measured, moderate or heavy drinking increased the induction dose requirements for thiopentone while the use of tobacco alone had no effect. Our results are in line with that report.

Intravenous anaesthetic induction causes rapid changes in the level of consciousness. Each evoked potential recording lasted about 60 sec. Thus, we could not measure anaesthetic "depth" in stable, stationary conditions. The patients may have been in lighter plane of anaesthesia at the end of the latest recording than the averaged waveform showed. We could have shortened the recording time by decreasing the number of averaged responses. However, we decided to average 500 responses to enhance the waveform reliability. The evoked responses of all patients were recorded in the same way, and nobody was awake during the study.

Smoking has been shown to increase the metabolism of many drugs. For instance, imipramine, theophylline and warfarin are metabolised faster in smokers than in non-smokers.[1,2] These drugs are metabolised mainly by cytochrome 1A and 2C subfamilies.[30] The isoenzymes responsible for the metabolism of thiopentone are not known. Previous studies have shown that longer-acting barbiturates phenobarbitone and hexobarbitone are metabolised at least partly by cytochrome 2 family.[31] However, whatever isoenzyme is mainly responsible for the metabolism of thiopentone, it does not appear to be affected by smoking. Cigarette smokers have greater upper airway reflex sensitivity and bronchial hyper-reactivity.[6,7] They are more likely to demonstrate laryngospasm, cough and airway obstruction than are non-smokers. Similar signs are sometimes associated with light anaesthesia.

Our study, using objective measures of anaesthetic adequacy, suggests that the altered pharmacodynamic or pharmacokinetic behaviour of thiopentone does not explain the greater incidence of laryngospasm and other airway problems in smokers.

In conclusion, thiopentone, 9 mg·kg⁻¹ LBM, caused cortical and haemodynamic depression, while cortical activity and haemodynamic variables were increased after a standardised stimulus of laryngoscopy and tracheal intubation. These responses were not affected by cigarette smoking. Pharmacokinetic analysis of thiopentone showed no difference between smokers and non-smokers. In this study cigarette smoking did not affect the pharmacodynamic or the pharmacokinetic behaviour of thiopentone.

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