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Quantitative EEG changes due to cerebral vasoconstriction. Indomethacin versus hyperventilation-induced reduction in cerebral blood flow in normal subjects

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Summary Hyperventilation leads to an increase in slow EEG activity as well as to a decrease in alpha activity. These effects may be considered a result of reduction in cerebral blood flow due to vasoconstriction, but metabolic factors, such as alkalosis and the increased formation of cerebral lactate, may also have to be taken into account. As indomethacin decreases cerebral blood flow it is possible to study cerebral vasoconstriction, without concomitant metabolic alkalosis or cerebral lactate formation.

Two parallel groups of 12 healthy male subjects (age 20–25) were studied with quantitative EEG (qEEG) and cerebral blood flow velocity as parameters. In the first group the effect of 100 mg indomethacin was studied. In the parallel group a standardized hyperventilation procedure was performed. In the indomethacin group the blood flow velocity decreased to 60% of the initial value; the qEEG showed a 0.5 Hz slowing of the alpha peak frequency ($P < 0.01$) and a decrease in the power of the alpha band without any change in the delta or theta band. In the hyperventilation group the blood flow velocity decreased to 63% of the initial value and the qEEG showed a marked increase in delta and theta activity ($P < 0.01$), but a non-significant change in alpha peak frequency.

Indomethacin and hyperventilation caused similar degrees of vasoconstriction; however, the increase in qEEG slow wave activity, which was observed only in the hyperventilation group, is apparently related to metabolic rather than haemodynamic factors.

Key words: Hyperventilation; Indomethacin; Cerebral blood flow velocity; Normal subjects; qEEG

One of the major problems when studying EEG changes in patients with cerebral ischaemia is the large inter-individual variability. As a consequence, a large patient population is required to study the quantitative EEG (qEEG) effects of ischaemia. Alternatively, a model may be used in which an identical hypoxic/ischaemic stimulus is imposed on a homogenous population. In a previous report a hypobaric hypoxia model was presented (Kraaier et al. 1988a); however, a major disadvantage of this model is that hypoxia is a stimulus for cerebral resistance vessels to dilate, leading to an increase in cerebral blood flow (CBF) (Lassen 1982), whereas in patients with cerebral ischaemia CBF — at least locally — is decreased.

A large decrease in CBF — down to 40% of the initial value — can be obtained by forced voluntary hyperventilation (HV). In the HV-induced model of reduced cerebral blood flow a marked increase in delta and theta activity, as well as a decrease in alpha activity, was described (Kraaier et al. 1988b). It is uncertain to what extent these EEG changes are due to reduced cerebral blood flow, to metabolic factors such as alkalosis or lactacidosis (Van Rijen et al. 1989) or to a combination of these.

Indomethacin — a non-steroid anti-inflammatory drug (NSAID) — decreases CBF by 30–50% (Pickard and Mackenzie 1973; Sakabe and Siesjö 1979; Quintana et al. 1983; Wennmalm et al. 1984; Lauritzen et al. 1987). This effect of indomethacin offers the opportunity to establish a human, pharmacological model of reduced cerebral blood flow, without the occurrence of alkalosis or cerebral lactate formation (Van Rijen et al. 1990).

These two models are compared in the present study. The effect of a single oral dose of 100 mg indomethacin was studied in 12 male students. In a parallel group of students the standardized HV procedure (Kraaier et al. 1988b) was modified such that there was a similar degree of vasoconstriction. Quantitative EEG and cerebral blood flow velocity (BFV) were studied as functional parameters in both groups.

Subjects and methods

Subjects

Two separate groups of 12 healthy, non-smoking male students were studied. The mean age was 23.2

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(S.D. 2.6) in the indomethacin study and 22.3 (S.D. 2.0) in the HV study. Prior to the study, each subject signed an informed consent form.

Methods

Instrumentation

EEG. Silver/silver chloride electrodes were attached to the skin with collodion. The following 3 derivations, based on the international 10/20 system, were selected: F4-C4, T4-T6 and P4-O2. Only right-sided derivations were used, thereby permitting simultaneous measurement of BFV with transcranial Doppler sonography on the left side. The EEG was recorded with a bandwidth of 0.26–30 Hz (−3 dB). The technician was constantly in touch with the subjects to keep them in a state of quiet attentiveness. Artifacts due to blinking, movement or muscle activity were reduced to a minimum by proper instruction of the subjects. Moreover, rejection of 2.5 sec epochs contaminated by artifacts could be accomplished online by the technician. EEG signals were fed directly into the computer for spectral analysis at a sampling frequency of 100 Hz (frequency range 0.7–24.1 Hz). An analysis time of 102.4 sec (20 epochs of 5.12 sec) constituted the spectra during HV. The effective frequency resolution was 0.59 Hz.

Capnography. An infra-red gas analyser was used for capnographic control. Continuous sampling of exhaled gas from a mouthpiece was accomplished at a flow rate of 500 ml/min through a side tube of 140 cm length. The nose was closed with a noseclip.

Transcranial Doppler sonography. BFV was measured with an EME-TC 2-64 apparatus. The mean flow velocity from the left middle cerebral artery (MCA) was measured, according to the method described by Aaslid et al. (1982). The part of the MCA giving the highest Doppler velocity was chosen as a site to record the BFV.

Procedure

Baseline records of qEEG and BFV were obtained in both models.

(I) Indomethacin model. Subjects ingested 100 mg indomethacin. After 90 min the qEEG and BFV were recorded again.

(II) HV model. The HV procedure was performed as described earlier (Kraaier er al. 1988b; Vriens et al. 1989) except that the end-tidal pCO_2 was 3 kPa (instead of 2 kPa in former studies) to obtain a similar degree of vasoconstriction as in the indomethacin model. The qEEG and BFV were recorded during the fifth minute of HV.

qEEG variables

As in previous studies (Van Huffelen et al. 1980, 1984; Wieneke et al. 1980; Kraaier et al. 1988b; Van der Worp et al. 1991) a number of qEEG variables were examined. Mean spectral frequencies, power densities and alpha peak frequencies were studied. Alpha peak centred spectra were also studied (Schwibbe et al. 1981). The alpha peak frequency and the 6 neighbouring 0.6 Hz bands were investigated to assess changes in the alpha frequencies around the alpha peak frequency. Subtraction spectra, consisting of the log power density difference curves between two spectra, each representative of one condition, were also studied. The conditions compared were the indomethacin condition versus baseline and the HV condition versus baseline.

Statistics

Wilcoxon's matched-pairs ranked signed (2-sided) test was used for statistical analysis.

Results

(I) Indomethacin model

BFV

The BFV was decreased to 60% (S.D. 10) of the initial value (Table I).

qEEG

Data for 11 subjects were available for qEEG analysis. There were no changes in the log power density of the delta and $theta_1$ bands. The log alpha power after indomethacin decreased ($P = 0.06$). The differences in the alpha frequencies, however, were far more pronounced: the mean alpha frequency decreased by 0.27 Hz ($P < 0.01$) and the alpha peak frequency by 0.53 Hz ($P < 0.01$) after indomethacin (Table II). These changes are readily demonstrated in the subtraction spectrum (Fig. 1), which shows no changes in the low frequencies but a pronounced effect in the alpha range. The lower range of the beta band was also slightly decreased. The alpha peak centred power spectra showed even more clearly a selective diminution of the alpha frequencies above the alpha peak frequency (Fig. 2). The power decrease in the 3 higher alpha bands adjacent to the centre band was about 3 dB more than that of the 3 lower alpha bands adjacent to the centre.

TABLE I

BFV in the middle cerebral artery in the indomethacin model (N = 11) and HV model (N = 12) (mean values and S.D.).

Model	Indomethacin	HV
Baseline BFV (cm/sec)	77 (6)	68 (11)
BFV during provocation (cm/sec)	44 (7)	43 (7)

TABLE II

Mean differences (S.D.) between indomethacin or HV and baseline qEEG parameters for the P4-O2 derivation. The significance of the values is indicated by ** $P < 0.01$ or * $0.01 < P < 0.05$. Under column heading P the significance of the difference between indomethacin and HV values is presented.

Model *	Indomethacin	HV	P
MP delta (dB)	−0.28 (1.52)	2.93 (3.40) *	0.009
MP theta (dB)	0.34 (0.92)	3.09 (2.99) **	0.009
MP alpha (dB)	−2.53 (3.93)	−2.52 (2.55) **	0.995
PF alpha (Hz)	−0.53 (0.51) **	0.18 (0.39)	0.002
MF alpha (Hz)	−0.27 (0.31) **	0.08 (0.28)	0.010

MP delta and MP theta indicate mean logarithmic power density in the delta (1.3–3.0 Hz) and theta bands (3.0–6.0 Hz). MP alpha indicates mean logarithmic power density in a 2.0 Hz band centred on the individual alpha peak frequency in dB. MF alpha indicates change in mean frequency of the alpha band (7.7–12.4 Hz) in Hz. PF alpha means change in peak frequency of the alpha band (7.7–12.4 Hz) in Hz.

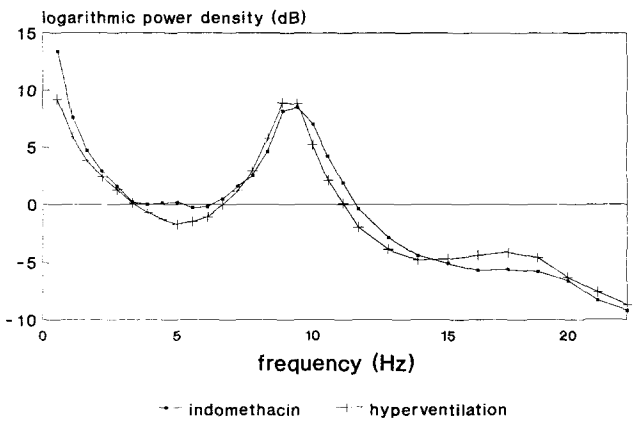

Fig. 1. Mean baseline spectra of absolute logarithmic power density for the P4-O2 derivation in the indomethacin model (N = 11) and the HV model (N = 12).

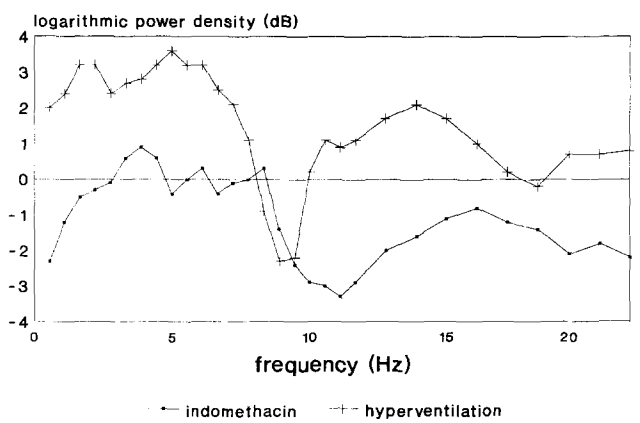

Fig. 2. Subtraction spectra of absolute logarithmic power density for the P4-O2 derivation in the indomethacin model (N = 11) and the HV model (N = 12).

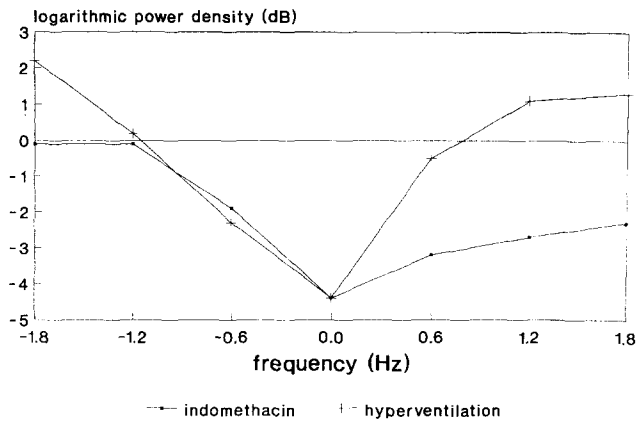

Fig. 3. Subtraction of absolute logaritmic power density of seven 0.6 Hz frequency bands centred on the individual peak frequency of the alpha band (7.7–12.4 Hz) for the P4-O2 derivation in the indomethacin model (N = 11) and the HV model (N = 12).

(II) HV model

BFV

Because of the chosen HV procedure, the BFV decreased to 63% (S.D. 7%) of the initial value (Table I), similar to the change in the indomethacin model.

qEEG

The log power density in both low frequency bands (1.3–6.0 Hz) showed a highly significant ($P < 0.02$) increase after HV. The increase was significantly different from that observed in the indomethacin model ($P < 0.01$) (Table II). The log alpha power decreased significantly ($P < 0.01$) after HV, to an extent similar to that observed in the indomethacin model. There were, however, significant differences in the alpha frequency variables between the two models. The mean alpha frequency did not change after HV in contrast to the significant change observed in the indomethacin model. The alpha peak frequency, which showed a significant decrease of 0.53 Hz in the indomethacin model, did not change in the HV model. The overall differences between the indomethacin effect and the HV effect are more apparent in the subtraction spectra (Figs. 1 and 3). There was also an important difference in the absolute change in beta activity. The differences in slow activity and beta activity were less apparent when relative power density spectra were studied. The differences in alpha activity, however, were pronounced (Fig. 1). These differences are also obvious in the alpha peak centred spectra. There was an identical decrease in the power of the alpha bands below the alpha peak frequency. There was, however, a significant difference ($P < 0.001$) in the small frequency bands above the alpha peak frequency between the indomethacin model and the HV model. The HV model showed no selective diminution of higher alpha frequencies.

Discussion

Indomethacin is one of the non-steroid anti-inflammatory drugs (NSAIDs) most frequently studied in animals and man. Its cardiovascular effects differ to some extent from those of other NSAIDs because, apart from inhibiting prostaglandin formation, indomethacin acts as a direct vasoconstrictor (Wennmalm et al. 1984). Administration of indomethacin decreases blood flow in the splanchnic region, the kidneys and the brain. Cerebral blood flow has been reported to be lowered by 30–50% (Lauritzen 1987). Other NSAIDs, at least aspirin and naproxen, are completely devoid of similar actions on the cerebral circulation (Quintana et al. 1983; Wennmalm et al. 1984). Because of the vasoconstrictor properties of indomethacin, it has been possible to establish a model of reduced cerebral blood flow in which BFV in healthy young subjects is decreased without concurrent alkalosis or excessive cerebral lactate production (Van Rijen et al. 1990), in fact without any clinically noticeable effect at all.

In the HV model (Kraaier et al. 1988b) the increase in delta and theta activity has been attributed to cerebral ischaemia as a result of a 60% decrease in BFV, while the formation of excessive cerebral lactate has been considered to be a result of increased anaerobic glycolysis. Recently, it has been demonstrated that even a 40% decrease in BFV during mitigated HV leads to the formation of cerebral lactate (Van Rijen et al. 1989). In the indomethacin model, however, the same decrease in BFV did not lead to lactate formation (Van Rijen et al. 1990). The qEEG showed an increase in slow delta and theta activity in the modified HV procedure.

In the indomethacin model the visually assessed EEG generally shows no changes; only after spectral analysis do changes become apparent. These changes consist of a decrease in power in the alpha band and a decrease in mean alpha frequency and of alpha peak frequency; this last variable shows the most pronounced changes. In the study of Van der Worp et al. (1991), in which the effects of hyperventilation and hypoxia were compared, similar alpha power and alpha frequency changes were obtained with hypoxia. Moreover, these changes are also comparable to those found in patients with minor ischaemic disorders such as TIAs or RINDs (Van Huffelen et al. 1980, 1984). Thus, there are several arguments, based on data concerning BFV and qEEG, to underline the relevance of the indomethacin model as a model of transient hypoxia/insufficient cerebral blood flow in man.

One might argue that there are several alpha rhythm generators. On the basis of principal component analysis, at least two alpha components have to be differentiated (Herrmann et al. 1978). Both experimental and clinical results could be explained by assuming that the higher alpha frequency generator is more susceptible to hypoxia/insufficient cerebral circulation.

The EEG findings during HV are completely different from those in the indomethacin model. The marked increase in slow activity during HV cannot be attributed to vasoconstriction alone, because the same degree of constriction in the indomethacin model did not induce changes in slow activity. It is possible that the HV-induced EEG changes are related to alkalosis and/or lactate formation (Van der Worp et al. 1991). The formation of cerebral lactate during HV can be explained by an increase in phosphofructokinase activity due to alkalosis (Norberg 1976). It is interesting to note that there is not only a large amount of slow wave EEG activity but also increased lactate formation in patients with severe cerebrovascular accidents.

With respect to the variables in the alpha band, there were no resemblances between the indomethacin model and the HV model: in fact, there were striking contrasts. For these reasons the indomethacin model appears to be superior to the HV model for the study of a decrease in cerebral blood flow.

One problem concerning the indomethacin model should be mentioned: the indirect effects of vasoconstriction on the EEG might be biased by some unknown direct drug effect on the EEG. However, such an effect is not known for other NSAIDs, which are devoid of an action on the blood vessels (Quintana et al. 1983; Wennmalm et al. 1984). Single doses of aspirin (0.65, 1.28 and 1.95 g showed no effects on qEEG and cognitive functions (Luria et al. 1979; Fink and Irwin 1982). NSAIDs also appear not to affect vigilance. Therefore a direct EEG effect of indomethacin seems to be unlikely.

In conclusion, the indomethacin model can be considered as an interesting human model of reduced cerebral blood flow, based on cerebral vasoconstriction. It might be used to study the effects of newly developed anti-ischaemic drugs with possible protective effects on brain function during ischaemia. The effects of HV in this context are more complex, because of the concurrent actions of vasoconstriction and several metabolic factors, which makes this model less preferable to the indomethacin model.

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