PAIN DURING CONTINUOUS NITROUS OXIDE ADMINISTRATION

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SUMMARY

The continuous administration of nitrous oxide, in subjects who remain conscious, caused only a relatively small increase in the threshold of appreciation of pain, induced experimentally by tibial pressure and a hot wire applied to the thenar eminence. The threshold reached a maximum at 10 min. A concentration of 50% nitrous oxide caused only a marginally greater effect than 33%. In some subjects pain thresholds returned to control values during administration of the gas. In contrast, when a concentration of 50% nitrous oxide was approached in step changes of 7–10% over a period of 45 min, the effect on the pain threshold was more than doubled. It was concluded that, with respect to analgesia, adaptation of the nervous system to a constant concentration of nitrous oxide can occur in some subjects.

Since the original observation by Davy (1800) there have been many studies showing that nitrous oxide elevates the threshold at which a wide variety of stimuli are appreciated (Persson, 1951; Haugen, Coppock and Berquist, 1959; Burns, Robson and Welt, 1960; Clutton-Brock, 1960; Robson, Davenport and Sugiyama, 1965; Chapman, Murphy and Butler, 1973; Tomlin et al., 1973; Chapman, Gehrig and Wilson, 1975). Previous studies on sensory thresholds have been concerned with the demonstration of directional changes after the administration of nitrous oxide for 10–15 min when, because the gas rapidly reaches equilibrium with the brain (Kety and Schmidt, 1948), it is assumed that the level of intoxication is stable and hence measurements may be made in a steady state. Although the use of nitrous oxide administered continuously in obstetrics was described by Rives in 1922, there has been no objective assessment of possible changes in sensory thresholds during continuous administration of the gas.

METHODS

Observations were made on 10 healthy male subjects. The stimuli used to evoke pain were tibial pressure and the application of a hot wire to the thenar eminence. The methods of applying these stimuli have been described previously (Morgan, Whitwam and Page, 1973). At each stage, five measurements of the threshold for each stimulus were made on each individual. The end-point was taken as that stimulus which caused a sensation interpreted by the subject as being painful.

Nitrous oxide in oxygen was administered in one of three ways. In the first experiments, after allowing 30 min for the subject to settle, control measurements were made while breathing air. Oxygen was then administered through a Mapleson A circuit (Mapleson, 1954) including a 4-litre reservoir bag and a close-fitting face mask equipped with a non-return valve. After 15 min, further measurements of pain thresholds were made. Nitrous oxide in oxygen was then administered in increasing concentrations in a stepwise fashion from 25% through 33% and 40% to 50%. At each concentration 10 min was allowed for equilibration at the end of which further observations of pain thresholds were made during the next 1.5–2 min and while the subject continued to inhale the mixture. After a further 3 min the concentration was increased so that at each concentration below 50% the gas was administered for 15 min.

In further experiments, after control observations had been made while the subject was breathing oxygen, nitrous oxide was administered in increasing concentrations in a stepwise fashion from 25% through 33% and 40% to 50%. At each concentration 10 min was allowed for equilibration at the end of which further observations of pain thresholds were made during the next 1.5–2 min and while the subject continued to inhale the mixture. After a further 3 min the concentration was increased so that at each concentration below 50% the gas was administered for 15 min.

In further experiments, after control observations had been made while the subject was breathing oxygen, nitrous oxide was administered in a concentration of 33% in oxygen for 60 min and pain thresholds were measured at 10, 30 and 60 min.

Finally, the effect of 50% nitrous oxide in oxygen (Entonox) was observed. After control observations the gas was administered for a period of 20 min and, when possible, measurements of pain thresholds were made at 5, 10, 15 and 20 min. Not all subjects were able to co-operate during the administration of Entonox.

Pain thresholds were determined also at intervals of 10 min in subjects, in the experimental environment, in the absence of any drug administration or additional...
FIG. 1. Effect of nitrous oxide on pain thresholds for tibial pressure and hot wire. (A) Progressive increase in the concentration of nitrous oxide (administered for 15 min at each concentration). Measurements of threshold took 1.5–2 min starting after 10 min at each concentration. (B) 33% nitrous oxide administered for 1 h. (C) 50% nitrous oxide administered for 20 min. Tibial pressure is expressed in lbf (applied via a spring-balance through a screw 9 mm in diameter placed over the surface of the tibia). The hot-wire scale is in volts (applied through a wire stretched over a glass rod placed on the thenar eminence). Each point is the mean of five observations. The percentage changes are the mean changes relative to the control period averaged over the subjects. The $P$ values indicate the significance of the difference between the appropriate time and the control period after performing a two-way analysis of variance with replication of all the observations. $*** P < 0.001$; $** 0.001 < P < 0.01$; $* 0.01 < P < 0.05$; n.s. $P > 0.05$.

stimuli other than those caused by the threshold determinations.

In subjects who were used for more than one type of study an interval of at least 2 weeks was allowed to elapse between each experiment.

RESULTS

The same seven subjects took part in the first two studies. All seven subjects were able to co-operate when the concentration of nitrous oxide was 33% or less. However, at 40% one subject became anaesthetized and after 10 min administration in another subject the onset of narcosis prevented readings of tibial pressure although the hot wire threshold was determined (fig. 1A).

For the Entonox study only four of the original seven subjects were available and three new subjects took part. One of the original subjects could not co-operate after the administration of Entonox for 10 min although this subject had been able to tolerate 50% nitrous oxide when this was approached in step changes over a period of 45 min. Two other subjects became narcotized to the point of being unable to continue at 15 min and 20 min respectively. On each occasion tibial pressure readings had been obtained, but thereafter the subject became unable to co-operate for the measurement of the hot-wire thresholds (fig. 1C).

In each study nitrous oxide caused a much greater percentage change in the threshold for tibial pressure than in the hot-wire threshold.

During the continuous administration of 33% nitrous oxide (fig. 1B) there was a significant increase in the mean pain threshold, although this was not true for every subject. In three of the seven subjects, at 1 h, the mean tibial pain thresholds did not differ from the control values. A similar finding occurred in four of the seven subjects in respect of the hot-wire test. In the case of tibial pressure, compared with the control values, the maximum effect was observed at 10 min.
After the administration of 33% and 50% nitrous oxide for 10 min, the tibial pressure thresholds increased by 30.5% and 28.8%, respectively (fig. 1b, c) while for hot wire the comparable values were 1.7% and 4.2%. This study suggests that, in subjects who remain co-operative, Entonox has only marginally greater effects than 33% nitrous oxide on pain thresholds.

In the first study, as the concentration of nitrous oxide was increased, a progressively greater effect on the pain thresholds was observed (fig. 1a). Thus in the five subjects in whom co-operation was maintained, an increase in tibial and hot-wire thresholds of 74.1% and 19.1% respectively was attained when the concentration of nitrous oxide reached 50%. This contrasts with the effects of Entonox alone where the maximum increase was 35.4% for tibial pressure and 9.1% for hot wire (fig. 1c), which suggests adaptation to the effect of the anaesthetic.

In subjects breathing air, there was no change in the threshold for pain evoked by tibial pressure and by a hot wire for periods up to 1 h.

**DISCUSSION**

A step-wise increase in the concentration of nitrous oxide caused a progressive increase in the pain thresholds which reached a higher level than when the greatest concentration was administered from the start. In contrast, the continuous administration of a constant concentration of the gas caused no further increase in thresholds after approximately 10 min and even when administered in high concentration (50%) there was a smaller increase in pain threshold. Also, in five subjects who were relatively resistant to the effects of nitrous oxide, the percentage changes in pain thresholds which were achieved by the administration, for 10–15 min, of either 33% nitrous oxide or Entonox were similar and, at best, of the order of 33%. This would suggest that only when concentrations are used at which the subject is virtually unconscious can a high degree of analgesia be anticipated. A similar observation was made by Tomlin and his colleagues (1973) and more recently Chapman, Gehrig and Wilson (1975) have confirmed that 33% nitrous oxide has little effect on the detection of severe pain stimuli.

Latto, Molloy and Rosen (1973) considered that during labour there is a requirement for the continuous administration of nitrous oxide at a relatively low concentration which can be increased in anticipation of painful uterine contractions. Their main concern was the problem of increasing the concentration of gas in the blood with sufficient rapidity when starting from zero. The present study suggests that during long-term administration it is possible to enhance the analgesic effect of nitrous oxide by progressively increasing its concentration, which supports their opinion.

Recently, Kerr and others (1975) showed that although Entonox was better than air in the immediate relief of the pain of myocardial infarction, after 10 min the analgesic effect of Entonox declined so that it became no better than air.

It may be that, with respect to analgesia, the central nervous system develops tolerance to a constant concentration of nitrous oxide and that this is an acute phenomenon, apparent within 10 min. Increasing the concentration disturbs the compensatory mechanism and, at high concentrations, allows the development of a degree of analgesia greater than that which can be achieved by a similar concentration administered continuously. This deduction is supported by a recurrence of the subjective phenomena of light narcosis at each step change in the concentration of nitrous oxide in this study. These phenomena included perceptual changes in vision and hearing and in some subjects a sense of numbness in the face and hands. All the subjects hyperventilated while receiving nitrous oxide. However, the object of the study was to observe the effects of nitrous oxide when administered in a conventional manner and not to determine the contribution of changes in blood-gases to the analgesic state.

A prominent feature of this study was a loss of the sense of the passage of time by subjects breathing nitrous oxide. At the end of approximately one hour's administration of the gas all the subjects were unaware of the elapsed time, which disturbed some of them. This confirms the work of Robson, Burns and Welt (1960) who noted that the estimate of a period of 15 s could be as long as 80–90 s in subjects who breathed 30% nitrous oxide and that the effect of the gas tended to be exponential with time estimates approaching infinity as unconsciousness occurred.

Robson, Davenport and Sugiyama (1965) have suggested that pain caused by tibial pressure and by a hot wire constitute different types of input to the central nervous system, and which are handled by different neurological mechanisms. The greater effect of nitrous oxide on tibial pain indicates that this is "processed" by more complex central neuronal connections which differ from those concerned with the appreciation of pain from the hot wire.
There is a need for a truly objective assessment of the value of nitrous oxide as an "analgesic" agent in intensive care and in obstetric situations and this has been initiated by Kerr and his associates (1975). It would appear that a high degree of analgesia can be obtained only in subjects who are at the point of unconsciousness, and in view of the variability of the response to nitrous oxide the empirical use of a fixed concentration leaves much to be desired. For some types of pain, if the modest analgesia which can be obtained is regarded as worth while, the results of the present study suggest that the continuous administration of Entonox may have little advantage over a lower concentration such as 33% or 40%. It would appear that, during prolonged administration of nitrous oxide, the maximal degree of analgesia can be achieved by starting with a relatively low concentration of the gas, such as 25%, and increasing this in a step-wise manner when the clinical situation demands an increase in analgesia. For this purpose changes in concentration of the order of 10% would appear to be appropriate. However, Entonox is easy to use and provides oxygen therapy without the metering problems necessary to prevent either hypoxia or oxygen toxicity when the gases are mixed from separate cylinders.

REFERENCES


DOULEUR PENDANT L'ADMINISTRATION CONTINUE DE PROTOXYDE D'AZOTE

RESUME
L'administration continue de protoxyde d'azote sur des sujets qui restent conscients, n'a causé qu'une augmentation relativement faible du seuil d'appréciation de la douleur, provoquée expérimentalement par une pression tibiale et par l'application d'un fil de fer chaud à l'éminence thenar. Ce seuil a atteint son maximum après 10 min. La concentration de 30% de protoxyde d'azote n'a causé qu'un effet marginalement plus grand que la concentration à 33%. Sur certains sujets, les seuils de douleur sont retournés aux valeurs témoins pendant l'administration du gaz. Par contre, lorsqu'une concentration de protoxyde d'azote à 50% a été atteinte par paliers de 7% à 10% sur une période de 45 min, l'effet sur le seuil de la douleur a été plus que doublé. On en a conclu qu'en ce qui concerne l'analgesie, l'adaptation du système nerveux peut se produire à une concentration constante de protoxyde d'azote sur certains sujets.

SCHMERZ WAHREN ANDAUERNDER STICKSTOFFVERABREICHUNG

ZUSAMMENFASSUNG
Die andauernde Verabreichung von Stickstoff bei Personen, die bei Bewusstsein bleiben, verursacht eine nur kaum erhöhte Schmerzschwelle. In diesem Experiment wurde Tibialdruck und heisser Drahtdruck auf den Daumenballen angewandt. Die Schmerzschwelle trat maximal nach 10 Minuten auf. Im Gegensatz, wirkte ein 50% Stickstoffkonzentrat kaum mehr als ein Konzentrat von 33%. Bei einigen Versuchspersonen trat die Schmerzschwelle bei Gasabgabe wieder auf Normalwerte zurück. Jedoch ergab sich bei einem 50% Stickstoffkonzentrat, dass die Schmerzschwelle von 7–10%, für die Dauer von 45 Minuten, eine mehr als verdoppelte Schmerzschwelle. Es wurde daraus erschlossen, dass, was die Analgesie anbelangt,
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in einigen Individuen, eine Anpassung des Nervensystems an konstante Stickstoffkonzentration auftreten kann.

EL DOLOR DURANTE LA ADMINISTRACION CONTINUA DE OXIDO NITROSO

SUMARIO

La administración continua de oxígeno nitroso, en pacientes que permanecían conscientes, produjo sólo un relativo aumento en el umbral de la apreciación del dolor, inducido experimentalmente por presión tibial y por un alambre caliente aplicado en la eminencia tenar. El umbral alcanzó su máximo a los 10 minutos. Una concentración de oxígeno nitroso al 50% produjo sólo un efecto marginalmente mayor que el 33%. En algunos pacientes los umbrales del dolor volvieron a valores de control durante la administración del gas. Como contraste, cuando una concentración de oxígeno nitroso al 50% se aproximó en cambios graduales del 7 al 10% por más de un período de 45 min, el efecto del umbral del dolor fue superior al doble. Se llegó a la conclusión de que, en relación con la analgesia, la adaptación del sistema nervioso a una concentración de oxígeno nitroso puede producirse en algunos pacientes.