THE LEVELS OF NITROUS OXIDE ANALGESIA

BY

GEOFFREY D. PARBROOK
Aberdeen Royal Infirmary and University of Aberdeen, Scotland

SUMMARY

The literature on the effects of various levels of nitrous oxide is reviewed. The rapid uptake and excretion of the gas facilitates the recognition of four levels or zones depending upon the concentration used. In the lightest level of nitrous oxide, Zone 1, moderate analgesia is present with few side effects. In Zone 2 psychological side effects of dissociation are present in addition to more potent analgesia. With the third level of nitrous oxide, Zone 3, marked somnolence is present in addition to almost total analgesia and amnesia, but patient contact is still preserved. This zone is known as "analgesic anaesthesia". Patient contact is lost in the deepest level of nitrous oxide, that of light anaesthesia (Zone 4). In this level there is a risk of involuntary movements. In conclusion it is suggested that, of the four zones, the first, of moderate analgesia, is the one of greatest clinical use for analgesia though "analgesic anaesthesia" may prove to have special indications. The fourth zone is of use in modern anaesthetic techniques.

The analgesic potency of nitrous oxide and its lack of toxicity give it special advantages over narcotics and other analgesics. In addition, it is now easier to apply nitrous oxide analgesia with new techniques of administration based on premixed or piped gas supplies.

The degree of analgesia with nitrous oxide increases with the inhaled concentration but the incidence of side effects and other symptoms depends upon the level. Many workers have investigated and studied specific concentrations or levels of nitrous oxide and a comprehensive review of the full range of nitrous oxide analgesia can thus be made. It is hoped that it may aid in the clinical applications of the gas.

In order to assess the effects of a known concentration of nitrous oxide it is first necessary to consider the rapidity of the onset of its effects and the speed with which these are lost on ceasing to inhale the gas.

THE RAPIDITY OF UPTAKE AND EXCRETION

The effects of nitrous oxide on a patient will depend upon the tension of the gas which is acting on the brain. Consequently it is important to consider the rate of uptake of nitrous oxide and the achievement of equilibrium between the inspired concentration and effective concentration at the brain.

The factors involved in this equilibration and its rate have been investigated and reviewed by many workers (Kety, 1951; Severinghaus, 1954; Salanitre et al., 1962; Smith and Butler, 1963, 1964; Onchi and Araki, 1963; Eger, 1964; Epstein, 1964; Eger et al., 1966). The arterial blood concentration of nitrous oxide reaches an initial plateau concentration within 10 minutes of commencing inhalation of the nitrous oxide-oxygen mixture. The actual rate of this initial equilibration depends upon cardiac output, alveolar ventilation and upon the concentration of nitrous oxide inhaled, but normally after 10 minutes the arterial tension will be over 90 per cent of that inhaled. A slow continuous uptake of nitrous oxide then occurs and allows further approximation of inspired to arterial levels. The equilibration of the brain is rapid owing to its vascularity and consequently the effective nitrous oxide concentration at the brain has also achieved equilibrium within 10 minutes (Kety and Schmidt, 1948).

The fall of nitrous oxide tensions in the arterial
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Clinical findings are in agreement with these studies. The effects of the gas come on within a few minutes and are generally lost within 10 minutes of ceasing to breathe the gas.

The rapid onset of the effects of nitrous oxide may be of special benefit in instances in which pain relief is urgently required. The rapid loss of effects also renders nitrous oxide analgesia more controllable than is the case with other analgesics.

The rapidity of the action of nitrous oxide facilitates the recognition of the effects of various percentages of the gas. A chart illustrating these effects is presented (fig. 1).

In compiling this chart it is assumed that the nitrous oxide has been administered for a minimum of 10 minutes and is given without any serious degree of hypoxia or air dilution. The overall therapeutic range may be divided into two equal parts: a lighter plane of analgesia and a second plane of "amnalgesia" (Klock, 1951, 1955; Wasmuth and Hale, 1954; Tom, 1956, 1959). In amnalgesia both potent amnesia and analgesia are present.

The first plane (analgesia) may be subdivided into a light level in which moderate analgesia is obtainable without side effects (Parbrook, Rees and Robertson, 1964) and a deeper level in which psychological side effects of dissociation (Steinberg, 1956) occur together with other side effects. "Amnalgesia" also may be subdivided into "analgesic anaesthesia" (Federmesser, 1962; Petrovsky and Yefuni, 1965), in which patient contact is maintained, and the light anaesthetic level in which the patient ceases to respond to the spoken word.

Four zones can thus be distinguished, the word "zones" being used to avoid confusion with the four "planes" of anaesthesia.

THE FOUR ZONES OF NITROUS OXIDE ANALGESIA

Zone 1. Moderate analgesia (approx 6 to 25 per cent nitrous oxide).

Normal and full contact may be maintained with the patient. The principal effect of the gas is analgesia and the analgesic potency increases in accordance with the gas concentration (Seevers et al., 1937; Chapman, Arrowood and Beecher, 1943; Chambers and Schultz, 1945; Sonnenschein et al., 1948; Persson, 1951; Parkhouse et al.,
In experimental studies in volunteers Chapman, Arrowood and Beecher (1943) found that 20 per cent nitrous oxide was of similar analgesic potency to morphine 15 mg. These results are consistent with those found in patients with postoperative pain in which 25 per cent nitrous oxide was found to be more potent than morphine 10 mg (Parbrook et al., 1964).

Slight sedation or a feeling of relaxation is often noticed at this level of nitrous oxide (Frankenhaeuser, 1963; Ruben, 1966; Parbrook, 1966). In the author's studies in postoperative patients it was found that in 126 patients treated clinically with 25 per cent nitrous oxide, two showed marked sedation with a tendency to fall asleep if left undisturbed. Euphoria occurs occasionally. Nausea does not occur but pre-existing nausea may be aggravated (Parbrook, 1966).

Studies in volunteers showed that other senses, such as touch, hearing, vision and proprioception, were impaired in addition to pain by these levels of nitrous oxide (Burns, Robson and Welt, 1960; Legge, 1965) and that psychomotor activity may be slightly affected (Sonnenschein et al., 1948).

Patients who are seriously ill, as, for instance, after some form of cardiothoracic surgery, may show greater susceptibility to the effects of nitrous oxide. In such patients a satisfactory sedative and analgesic effect is sometimes obtained with as little as 10 per cent nitrous oxide.

The absence of serious side effects makes this zone of nitrous oxide analgesia particularly useful in instances when moderate pain relief is required.

Zone 2. Dissociation analgesia (approx. 26 to 45 per cent nitrous oxide).

As the concentration of nitrous oxide is increased above 25 per cent the patients experience psychological symptoms described by Steinberg (1953) as dissociation from the environment. These psychological effects have been extensively studied in volunteers (Sonnenschein et al., 1948; Steinberg, 1953, 1954, 1956; Russell and Steinberg, 1955; Parkhouse et al., 1960; Frankenhaeuser, 1963; Rodnight and Gooch, 1963; Berry, Gelder and Summerfield, 1965).

At the lower levels of this zone, e.g. 30 per cent nitrous oxide, psychological symptoms are mild and may take the form of a sense of drunkenness, dreaminess, a sense of detachment or a lack of ability to concentrate (Steinberg, 1956). The effects of such levels of nitrous oxide are generally regarded as pleasant, though in a study in volunteers a substantial minority found them unpleasant (Steinberg, 1956).

At higher concentrations, e.g. 40 per cent, the psychological effects become more pronounced. Perseverations may be seen, the volunteer repeating words or movements several times in succession, and a tendency to dream is often present. The marked inebriation occasionally seen with these levels of nitrous oxide was responsible for its alternative name of "laughing gas".

Marked analgesia is present, the degree of analgesia increasing in proportion with the rising nitrous oxide concentration (Seevers et al., 1937; Chambers and Schultz, 1945; Sonnenschein et al., 1948; Persson, 1951; Haugen, Coppock and Berquist, 1959; Parkhouse et al., 1960; Dundee and Moore, 1960; Dundee, Nicholl and Black, 1962). This analgesic effect may be potentiated by the sense of detachment which is often present, the patient noticing the pain but feeling that it is occurring outwith himself and is not of concern to him.

Other senses—touch, hearing and proprioception—are progressively impaired as the gas concentration is increased (Steinberg, Legge and Summerfield, 1961; Westerlund, Pittinger and Reger, 1961; Legge, 1965). In addition there is an altered time sense (Steinberg, 1955; Robson, Burns and Welt, 1960).

A light sedative effect is often seen in this zone, but full contact can be maintained with the patient although this may require conscious effort on the part of the latter. The presence of marked sedation and drowsiness with the higher levels of nitrous oxide indicates the onset of Zone 3—analgésic anaesthesia. The actual percentage of nitrous oxide required for this upper limit of Zone 2 is dependent on the patient but is generally about 40–50 per cent. Occasionally a person is found who is specially susceptible to nitrous oxide and will become unresponsive (Zone 4) with as little as 40 per cent (Seevers et al., 1937; Jacobs and Barron, 1942; Parkhouse et al., 1960; Robson, Burns and Welt, 1960). For this reason the percentages of nitrous oxide quoted can only be used as guides to the levels needed in the average patient.
Slight amnesia may be detected when 30 per cent nitrous oxide is inhaled (Steinberg and Summerfield, 1957) and increases as the concentration is increased (Robson, Burns and Welt, 1960; Frankenhaeuser, 1963). On the other hand, memory may be improved for events preceding nitrous oxide treatment (Summerfield and Steinberg, 1957).

Paraesthesia, a sense of impending unconsciousness, auditory effects and dizziness are other common side effects of these levels of nitrous oxide analgesia. There is usually a distinct time, 1–2 minutes after commencing inhalation, at which these subjective effects are particularly marked. The effects may lessen or even cease if the patient or volunteer continues to inhale the gas (Seevers et al., 1937; Chambers and Schultz, 1945; Tunstall, 1966, personal communication; Steinberg, 1967, personal communication).

Nausea is a rarer side effect reported in some but not all the studies. The risk of nausea appears to increase as the nitrous oxide percentage is raised (Parkhouse et al., 1960). Chapman, Arrowood and Beecher (1943) found a complete absence of nausea and vomiting with nitrous oxide although the same volunteers showed a high incidence of nausea and vomiting after morphine. Jacobs and Barron (1942) suggested that repeated “see-sawing from high to low” concentrations of nitrous oxide could cause nausea which would otherwise be absent.

**Zone 3. Analgesic anaesthesia (approx. 46 to 65 per cent nitrous oxide).**

At an average concentration of 45 to 50 per cent nitrous oxide, patients or volunteers developed marked amnesia (Gray, 1954; Robson, Burns and Welt, 1960; Hustead, 1964). Nevertheless spoken contact can be retained until a slightly higher percentage of nitrous oxide is inhaled and the person does not become unresponsive until concentrations of about 60 to 65 per cent are reached (Chapman, Arrowood and Beecher, 1943; Chambers and Schultz, 1945; Persson, 1951).

A zone is consequently identifiable in which the patient will respond to commands but will show near-complete amnesia. Marked somnolence and near-complete analgesia are also present. It is of interest that an analogous level of amnesia and analgesia has been described with ether anaesthesia (Artusio, 1955).

This level of nitrous oxide represents an in-between zone between analgesia and anaesthesia and has been widely used by Russian workers under the name of “analgesic anaesthesia” (Federmesser, 1962; Petrovsky and Yefuni, 1965). It was also used by Klock (1951) in his early studies with techniques of “amnalgesia”.

Minor surgical procedures may be performed in this zone, contact being maintained with the patient by the spoken word (Federmesser, 1962; Barth and Lüder, 1966) or by music (Cherry and Pallin, 1948). Too deep a level of nitrous oxide is revealed by loss of contact and is associated with the risk of involuntary movements (Federmesser, 1962; Barth and Lüder, 1966). To hasten the induction of analgesia most workers administer a high concentration of nitrous oxide initially, e.g. 80 per cent, and subsequently reduce the concentration according to the patient’s response. Although the average long-term maintenance concentration is normally between 45 and 65 per cent nitrous oxide, individual variation is seen and the percentages used may range from 30 to 80 per cent.

Hustead (1964) found similar variability in his studies of the use of nitrous oxide in obstetrics and this variability is in keeping with the studies of Frumin (1957) and Rosen (1959). These workers found that occasionally a patient retained partial memory during continuous administration of 50 to 60 per cent nitrous oxide. When such percentages of nitrous oxide are used for major surgery in association with relaxants the amnesic effect of nitrous oxide is apparently potentiated by the concurrent use of hyperventilation and complete amnesia results.

Some of the side effects reported in Zone 2, such as paraesthesia, appear to be absent or less pronounced but a tendency to dream persists (Cherry and Pallin, 1948; Frumin, 1957; Federmesser, 1962; Barth and Lüder, 1966). Nausea and vomiting were reported to occur in a few patients by Federmesser and by Barth and Lüder but since these patients had undergone minor surgical procedures the nausea may not have been related to the use of nitrous oxide. Nausea and vomiting was not reported in the patients of other workers with this level of nitrous oxide (Cherry
The assessment of consciousness within this zone is controversial. Subjectively the patient may afterwards regard himself as having been unconscious as he may have complete amnesia; consequently it may be reasonable to regard about 50 per cent nitrous oxide as providing unconsciousness (Gray, 1954). From the objective point of view, however, loss of consciousness may be placed at the upper limit of this zone, at about 60 per cent nitrous oxide (Chapman, Arrowood and Beecher, 1943; Chambers and Schultz, 1945; Persson, 1951) as the patient may still co-operate and reply to questions in this zone. Barth and Lüder also take the upper limit of the zone as the level of loss of consciousness.

Federmesser subdivides analgesic anaesthesia into three planes. In the lightest plane the psychological effects of dissociation analgesia are still present and the patient may experience a state of inebriation with a "kaleidoscope of images and thoughts, nearly always on one or another emotional theme". In plane 2, the somnolent state, as described above, supervenes. In the deepest plane, contact with the patient becomes very slight and there is a risk of involuntary movements. In this third plane "the patient under anaesthetic carries out only the most simple commands, and then, only when they are repeated several times".

If the percentage of nitrous oxide inhaled is further increased, contact with the patient is no longer possible and light anaesthesia supervenes.

Zone 4. Light anaesthesia (approx. 66 to 85 per cent nitrous oxide).

At this level of nitrous oxide contact with the patient is no longer possible and complete amnesia and analgesia are present. Light anaesthesia with 66 to 80 per cent nitrous oxide in oxygen was used first by Andrews (1868) but did not become popular owing to the instability of the anaesthetic state with the attendant risk of involuntary movements or even stage 2 anaesthesia delirium (Guedel, 1937).

Raginsky (1950, 1964) showed that the effects of nitrous oxide and the risk of the onset of delirium depended upon the mental state of the patient. In patients put at their ease he found that 80 per cent nitrous oxide provided adequate anaesthesia for dentistry. Klock (1955) and Tom (1956, 1959) have used "amnalgesic" techniques of this type, but exceptional expertise is required, and minor involuntary movements may occur. A marked conjugate deviation of the eyes is characteristic of this level of amnalgesia and Klock (1955) advocates the use of this level in conjunction with local block or infiltration anaesthesia in dentistry.

Bert (1883) introduced the use of 80 per cent nitrous oxide and 20 per cent oxygen to prolong the period of useful anaesthesia after inducing anaesthesia with 100 per cent nitrous oxide. Similar techniques in which nitrous oxide anaesthesia and hypoxia are combined are still in use in dental anaesthesia. Alternatively deeper levels of anaesthesia may be obtained without hypoxia if higher tensions of nitrous oxide are administered using a pressure chamber (Bert, 1879; Faulconer, Pender and Bickford, 1949).

As previously mentioned, the lower limit of this zone is variable, depending upon the patient, and in some cases light anaesthesia may be attained with concentrations of nitrous oxide much lower than 66 per cent. On the other hand, patient contact can sometimes be maintained when concentrations as high as 80 per cent are inhaled (Frumin, 1957; Barth and Lüder, 1966).

Amnesia is apparently complete with this level of nitrous oxide anaesthesia. Nevertheless caution is required before accepting that the patient is completely amnesic because studies using hypnosis have shown that the amnesia accompanying various types of anaesthesia can be broken (Cheek, 1959, 1966; Levinson, 1965). In Levinson's studies patients recalled events taking place during deep ether anaesthesia, while Cheek reported instances of unconscious perception of events with a variety of anaesthetic agents.

The advent of muscle relaxants has restored the usefulness of this level of nitrous oxide, light anaesthetic levels being used to maintain unconsciousness during surgical procedures. For such use the effects of the gas are usually potentiated by the use of hyperventilation.

Practical application of the zones of nitrous oxide analgesia.

In treating patients with nitrous oxide the correct levels of the gas may be obtained by several
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different techniques. The simplest system is the administration of an accurately known and controllable percentage of nitrous oxide by means of a tightly fitting facepiece, using a semiclosed or a non-rebreathing circuit. Alternative techniques make use of a higher percentage of nitrous oxide than that indicated in figure 1 and control the effective concentration of the gas either by limiting the number of breaths inhaled or by allowing air dilution of the inspired gas.

These zones should be identified by clinical signs rather than by placing reliance on fixed percentages of nitrous oxide, although the latter are useful as a guide, being most accurate at the lower levels of nitrous oxide analgesia. It is the tension of nitrous oxide which is important rather than the percentage and consequently a low barometric pressure (as at a higher altitude) will increase the percentage of nitrous oxide required. Even normal climatic fluctuations of barometric pressure may have a slight effect (Ruben, 1953).

With many anaesthetic agents a more potent effect is observed from a given blood level during induction than during maintenance or recovery. This effect is known as "acute tolerance" (Mirsky et al., 1941; Brodie et al., 1951; Dundee, Price and Dripps, 1956; Maynert and Klingman, 1960) and the degree of tolerance is related to the peak concentration of the agent concerned. The studies of Persson (1951) suggested that some degree of tolerance or "accommodation" does occur with nitrous oxide analgesia. Such an effect must develop in the early stages of induction because there is no evidence of a continuous lightening of the anaesthetic or analgesic state when a steady concentration of the gas is inhaled. Clinical experience shows that patients who habitually take alcohol or similar drugs can develop chronic tolerance to anaesthetics such as nitrous oxide (Bert, 1879; Bourne, 1960) and relatively higher percentages of the gas may be needed.

The effects of nitrous oxide analgesia are modified by the concurrent use of other agents. The hypnotic effect is increased if barbiturates or other sedatives have been used, whilst the analgesic effect is greater if the patient has received a narcotic prior to the use of nitrous oxide (Parbrook, 1966). Atropine and hyoscine, on the other hand, have an antanalgesic action (Christensen and Gross, 1948; Gross et al., 1948; Dundee, Nicholl and Moore, 1961) and should therefore be avoided. Studies by Persson (1951) of nitrous oxide analgesia showed that concurrent hypoxia can give additional analgesia, and that a high inspired oxygen percentage (over 70 per cent) can slightly antagonize the nitrous oxide analgesia.

Finally, the effects of nitrous oxide may also be modified by the patient's environment or by preconceived ideas because inhalation of the gas induces a state of increased suggestibility (Lassen, 1964). Thus if volunteers expect to fall asleep with 30 per cent nitrous oxide a high proportion will in fact do so (Steinberg, 1967, personal communication).

Other effects of nitrous oxide.

In applying nitrous oxide analgesia several other effects of the gas must be considered.

When nitrous oxide is inhaled continuously for several days leucopenia occurs due to marrow toxicity (Lassen et al., 1956). It is wise, therefore, to limit the duration of continuous treatment with nitrous oxide to a maximum of 24 hours. This leucopenic effect is discussed in greater detail elsewhere (Parbrook, 1967).

Less serious side effects of nitrous oxide include a slight peripheral vasodilatation, particularly of the veins (Eastwood, 1964), and perhaps an increased digital blood flow as indicated by the digital pulsation volume (Smith and Butler, 1964). There may be some increase of tidal ventilation in postoperative patients (Petrovsky and Yefuni, 1965; Pugachev and Kolygin, 1965) probably due to relief of wound pain.

Diffusion effects may be important in some circumstances of nitrous oxide treatment. During induction nitrous oxide may diffuse into encapsulated pockets of air in the body and increase their volume. Abdominal distension may therefore be increased (Eger and Saidman, 1965) and special difficulties may arise in patients with a pneumothorax (Hunter, 1955) or after air encephalography (Saidman and Eger, 1965) or in patients in whom there is a risk of air embolism (Nunn, 1959; Munson and Merrick, 1966). Outward diffusion of nitrous oxide at the end of treatment or anaesthesia will dilute the inspired air and lead to a temporary "diffusion anoxia" (Fink, 1955). These diffusion effects are greater with the higher
or anaesthetic concentrations of the gas and are less important with the analgesic levels.

CONCLUSIONS

The most useful level of analgesia is probably the lightest level (Zone 1) owing to the absence of undesirable side effects. The disadvantage of this level is that only moderate analgesia is obtainable though this may be increased by the concurrent use of a narcotic such as methadone (Parbrook, 1966).

A slightly deeper level of nitrous oxide analgesia is useful in many patients but has the disadvantage that a few of them may find the side effects unpleasant. In cases in which light levels of anaesthesia are inadequate, analgesic anaesthesia (Zone 3) may be satisfactory. Use of this level differs from that of the lightest level in that closer supervision and greater expertise are required.

Light anaesthesia (Zone 4) is principally of value as a part of modern anaesthetic techniques in association with relaxants.

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**LES TAUX D'ANALGESIE AU PROTOXYDE D'AZOTE**

**SOMMAIRE**
Un aperçu est donné de la littérature au sujet des effets de divers taux de protoxyde d'azote. L'absorption et l'excrétion rapides du gaz permettent de reconnaître aisément quatre taux ou zones, qui dépendent de la concentration employée. Au taux inférieur de protoxyde d'azote, Zone 1, il y a une analgésie modérée avec peu d'effets secondaires. Dans la Zone 2, des effets secondaires psychologiques de "dissociation" accompagnent une analgésie plus profonde. Avec le troisième taux de protoxyde d'azote, Zone 3, il existe supplémentairement à une analgésie et amnésie quasi complètes, une somnolence marquée, mais le contact avec le patient persiste. Cette zone est connue comme "anesthésie analgésique". Le contact avec le malade se perd avec le taux le plus élevé de protoxyde d'azote, celui d'"anesthésie légère" (Zone 4). Dans cette zone, il existe un risque de mouvements involontaires. On suggère en conclusion que parmi les quatre zones, la première d'"analgésie modérée", offre la plus grande utilité clinique d'analgésie, quoique l'"anesthésie analgésique" peut avoir certaines indications spéciales. La quatrième zone trouve son application dans les techniques modernes d'anesthésie.

**STADIEN DER LACHGAS-NARKOSE**

**ZUSAMMENFASSUNG**