ENTONOX®

Conquering procedural pain
For more than 160 years*

Arthur Ernest Guedel (1911)

Gardner Quincy Colton (1867)

Horace Wells (1844)

Micheal tunstall (1961)

Joseph Priestly (1775)

Humphry Davy (1799)

*ENTONOX® contains nitrous oxide which has been used in clinical practices for more than 160 years.

Contents.

ENTONOX® is a fast-acting inhaled analgesic

ENTONOX® is a patented pre-mixed pain-relievuing gas of 50:50 nitrous oxide (N_2O) and Oxygen (O_2). The gas is contained in a blue with a white and blue shoulder and deliever to the patients via inhalation by using a pressure regulator and demand valve.

ENTONOX® is both highly effective and controllable in its effects:

- rapid onset and rapid recovery
- do not accumulate to any great extent within the body
- free from after-effects of the risk of overdose
- compatible with all other analgesic or therapeutic drugs
- effects are predictable, controllable and relaible

…. continue the heritage of Nitrous Oxide which has been proven for more tha 160 years

Nitrous oxide was discovered and purified in the mid 1700's. it has been used medically since 1844. Today, it is an essential ingredient in anesthetic which is an ideal agent for the treatment of short-term pain; including

- 1775 - First synthesised by Joseph Priestley
- 1799 - First self-medication by Humphry Davy
- 1844 - First used medically to reduce pain during wisdom tooth extraction by Horace Walls
- 1860s - Popular in USA
- 1867 - Introduced to Europe and first used as a general anesthetic in surgical medicine by Gardner Quincy Colton
- 1911 - First patient-controlled analgesia technique was described by Arthur Ernest Guedel
- 1961 - N_2O/O_2 system was developed by BOC Healthcare and first used in obstetric practice by Micheal Tunstall
- 1970 - Use of ENTONOX® in ambulance services was introduced by Peter Baskett
- Today - ENTONOX® is the mainstay of analgesia for childbirth and pain relief in acute situations

Nitrous Oxide (N_2O) is the longest serving member of the anasthesiologist's pharmacologic armamentarium.

Central acting analgesic with the release of endogenous neurotransmitters

Nitrous oxide acts centrally within the pain centers of the brain and spinal cord causing the release of endogenous neurotransmitters (eg. Opioid peptides and serotonin) and the activation od certain opioid receptors.

The theories of the molecular mechanism to account for nitrous oxide's anasthetic and analgesic actions are summarised as follows:

Macanism of anasthetic action

- non-competitive inhibition of NMDA (N-methyl-D-aspartate) subtype of glutamate receptors
- activation of two pore domain potassium channels, eg. TREK – 1 channel

Mechanism of analgesic action

- activation of descending noradrenergic pathways due to the release of opioid peptides in the peri-aqueductal gray matter of the midbrain

The use of ENTONOX® produces a more relaxed patient and complete recovery of the patient from inhalation takes a matter of minutes.

Fast-acting and short duration analgesic without prolonging effects

ENTONOX® has unique pharmacological effects which calls for its use in medical practice for decades.

Rapid onset / fast-acting

- effects are apparent within 4-5 breaths; about 20 seconds
- maximum effects within 2-3 minutes of inhalation
- inhalation is commenced shortly before the desired analgesic effect is required

Rapid offset / fast recovery

- once inhalation stops, arterial concentration of nitrous oxidfe reduces 35% in 30 seconds
- analgesic effects wear off quickly within a few minutes cessation of inhalation
- speedy reversal of effects when required

Duration of action depends on the duration of inhalation

- inhalation is continued throughout the painful aspects of the procedure, or for as long as the analgesic effects is desired

Do not accumulate to any great extent within the body

- low solubility in water and fat, therefore low accumulation in fat and tissues
- do not combine with haemoglobin

Extremly stable and is essentially not metabolized by the body

- eliminate essentially unchanged via lungs (expiration)

Proven effective analgesic with mild to moderate sedative and anxiolysis effects

Efficacy of ENTONOX® is proven. It has been used widely in many clinical areas in hospitals (eg. Labour room, accident and emergency departments, hospital wards and clinics) and in the ambulance services. ENTONOX® has also not only been as a sole analgesic in clinical practice successfully but also in combination with other analgesic.

Effective analgesic' , sedative and anxiolysis

- relieve acute pain and discomfort due to injury and short procedures (medical intervention, investigation and treatment) among paediatrics and adults, including
  - *colonoscopy*
  - *fracture manipulation*
  - *venous cannulations*
  - *laceration repair*
- produce a more relaxed patient

Analgesic & sedation effects are comparable with other agents

ENTONOX® is as effective as

- 100mg pethindine
- meperine + promethazine
- pethdine + midazolam

Used in combination with other analgesic

- allow dose reduction of other agents such as morphine and pethidine
- reduce potential side effects associated with other agents

Consideration for use of ENTONOX®: side effects and contaminations

Side effects associated with the correct short-term use of ENTONOX®

Side effects experienced are minimal and wear off quickly, Moreover, it is completely reversible When inhalation is stopped. Common side reported are:

- mild nausea and vomiting; especially among indivials who are prone to emesis
- diziness
- amnesia

Side effects during prolonged exposure

Exposure to ENTONOX® exceeds a total of 24 hours or more frequently than every 4 days will:

- inactive vitamin B12 (inhibition of enzyme methionine synthesis)
- interfere folate metabolism
- impair DNA synthesis

The above interferences will result in:

- *megaloblastic marrow changes*
- *agranulocytosis*
- *sub-actue combined degeneration*
- *leucopenia*
- *myeloneuropathy*

Contraindications

Nitrous oxide will diffuse rapidly into the space and thus increase its size. Hence, ENTONOX® should not be used in any condition where air is entrapped within the body and where its expansion might be danerous. For example:

- *artificial, traumatic or spontaneous pneumothorax*
- *air embolism*
- *severe bulluos emphysema*
- *decompression sickness*
- *following a recent dive*
- *following air encephalography*
- *during myringoplasty*
- *gross abdominal distension*
- *in patients having received recent intraocular injection (eg. SF)*
- *head injuries with impairmeant of consciousness*
- *maxillofacial injuries*

Simple, non-invasive, patient-controlled, safe and on-demand basis mechanism of delivery

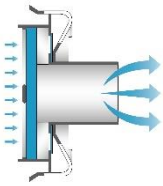
ENTONOX® is delivered to the patients easily via inhalation which is non-invasive, Patient-controlled, safe and on-demand basis.

- administered via a face mask or mouthpiece attached to a demand valve system
- designed for self-administration by the patient under medical supervision
- can be used safely in combination with other opiated or other analgesic

Demand valve: enables self-regulated pain relief

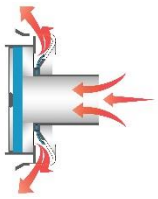
The basis of the inhalation unit is the demand valve. The benefits of the demand valve are:

- easy to use
- deliver the gas mixture to the patient at appoximate atmospheric pressure
- ensure the gas will not flow when the cylinder is turned on unless a negative pressure is produced via face mask or mouthpiece and tubing
- prevent expired breath entering the handset
- the amount of gas released is determined by the patient
- ensure the patient will not receive an overdose of gas because the face mask or mouthpiece will drop off when patient becomes drowsy



Inhalation

Negative pressure is produced via face maskor mouthpiece and tubing. The demand valve opens and the gas is delivered.



Exhalation

The demand valve closes and the expired gas passes out via the expiratory valve on the handpiece. This prevents expired gases from entering the handset.

ENTONOX®: Simle to use under medical Supervision

Preparation:

- ensure all the necessary equipments are prepared: cylinders and demand valve system
- check the patient has no contraindications and ensure the room is adequately ventilated
- make sure the patient can understand simple instructions and is able to handle the demand valve apparatus
- ensure the patient is in comfortable position

Patient instruction:

- demonstrate the demand valve apparatus to the patient
- explain to the patient:
  - *he or she is in control*
  - *breathe an and out regularly and deeply (not faster than normal) through face mast or mouthpiece*
  - *stop inhaling, if he or she feels drowsy*
  - *encourage he or she to practice before the procedure to get corrected technique*

Used and monitoring:

- start any procedure after the patient has inhaled ENTONOX® for a short period of time
- observe the patient throughout the procedure for level of pain and any side effects
- direct the patient to rest and cease inhaling at appropriate stages or when they become drowsy
- if the patient hyperventilates, encourage the patient to exhale slowly
- if the patient falls unconcious, the face mask or mouthpiece will fall away from the patient's hands and normal breathing will recommence

End of procedure:

- at the end of procedure, cease inhalation by removing the deamnd valve equipment and turning off the cylinder
- ensure the patient is comfortable and continue to observ the level of consciousness
- wait until any drowsiness or giddiness has subsided before allowing the patient to be moved
- record the ENTONOX® admission on the patient's prescription chart; noting any side effects experienced

ENTONOX® and clinical therapy

Obstetrics:
Childbirthand obstetrical procedures

Examples:

- *removal of a placenta*
- *vacuum extraction orfroceps on a women with epidural*
- *manual rotation of an occiput posterior fetus per vagina*

Relieve pain during childbirth and when pain relief for a procedure is suddenly needed

- ease of use, non-invasive, self-regulated, short-term inhaled analgesic
- reduce the level of pain and anxiety without undue sleepiness
  - *mothers can participate in delivery actively and remain in control during labour*
- self-administered under supervision
  - *allow mothers to adjust their intake to suit their own indiviual pain thersholds and comfort levels.*
- Eliminate rapidly from the body through lungs
  - *do not accumulate in the mothers' and babies' bodies*
- Have no known negative effects on the babies during childbirth
- Do not depress respiration
- High oxygen content in the bloodstream is delivered to the babies

Nothing is as quick as ENTONOX®; in its absence, some women have to endure the paindful obsterical procedures without any pain relief

Emergency & Pre-hospital care:

Ambulance services, Accident & Emergency Departments

Example:

- *fracture manipulation*
- *wound dressing changes*
- *venopuncture*
- *patient mobilisation*
- *dermatological procedures*
- *suturing of lacerations*
- *orthopaedic joint manipulation*
- *radiological procedures*
- *endoscopy*
- *burns dressing*
- *vascular procedures*
- *wound drain removal*

Control pain (alone or in combination) due to short procedures via simple-to-use non-invasive mechanism of delivery

- immediate effective pain relief (rapid onset and rapid recovery)
- alternative to commonly used analgesic agents (morphine, pethidine, NSAID's)
- when used in combination with other analgesic, it allows dose reduction of these drugs and thus reduces potential side effects associated with them
- do not mask signs and symptoms that may later be necessary for definitive diagnosis of the injury or illness
- ease of use, non-invasive and self-administered
- high patient acceptence
- calm down the patients
- minimal side effects

Entonox® for painful procedures

Paediatrics:

Surgical and medical

Example:

- *surgical dressing*
- *burn dressing*
- *venous cannulation*
- *nerve conduction study*
- *endoscopy*
- *dental care*
- *short minor procedures*
  eg. Lumbar puncture, bone marrow aspiration, percutaneous biopsies
- *emergency*
  eg. Laceration repair, bladder catheterisation, fracture with minor displacment

Relieve pain and anxiety of the children during painful procedures

- reduce pain and anxiety
- reduce distress of children and hence provides comfort for parents
- distraction strategy for nursing staffs
- rapid recovery: mean recovery is 3 minutes
- reduce procedure time
- ease of use and non-invasive nature of administration
- very low incidence of side effects

By using ENTONOX® for procedural pain in children, it is possible to break the cycle of fear in a simle way. This allows doctors to take many treatments that are necessary; but would otherwise be very difficult if the children are too afraid and feel too much pain.

Adults:

Surgical and medical

Example:

- *colonoscopy*
- *removal of nasal packs*
- *outpatient surgery*
- *intra-ocular implants*
- *vascular and interventional procedures*
- *acute myocardial ischemia*

Reliable effective rapid pain relief with conscious sedation

- effective analgesic with conscious sedation
- rapid onset and fast recovery
  - *recovery time after colonoscopy was reduced by 37 minutes compared to IV ketobemidone / midazolam*
- reduce time to discharge
- ease of administration
- minimal side effects
- good patient acceptability

Denistry

Example:

- multiple fillings
- root canal treatment
- extraction
- crowns

Relieve pain with minimal sedation during dental treatment

- relieve pain with rapid onset
- flexible duration
- quick recovery time – rapid resumption of normal activities
- patients are in total control
- simple, non-invasive, patient-controlled and safe administration
- very few adverse effects

ENTONOX®: Abbreviated prescribing information

Name of product: ENTONOX® (oxygen 50%, nitrous oxide 50%)

Pharmaceutical form: Compressed medical gas (for medicinal use only)

Indications: Relief pain in acute trauma, dental work, pianful procedures suc as burn dressing, wound debridement, suturing, normal labour, and acute surgical or medical contitions

Method of administration: ENTONOX® is administered via inhalation by the patient himself under supervision of trained medical personnel or may be administered by attendant medical personnel. Doses are self-regulated.

Contraindication: ENTONOX® should not be used in any condition where is entrapped within a body and where its expansion might be dangerous.

Special warning and precautions for use: Avoid prolonged or frequent exposure of ENTONOX®. ENTONOX® should be used for more than a total of 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring. Scavenging of waste gases should reduce operating theatre and equivalent treatment room levels of ambient nitrous oxide to a level below 100ppm. ENTONOX® is non-flammable but strongly supports combustion and should not be used near sources og ignition. Under no circumstances should oils or gases be used to lubricate any part of the ENTONOX® cylinder or the associated equipment used to deliver the gas to the patient.

Pregnancy : There is no published material that shows nitrous oxide is toxic to the human foetus, therefore, there is no absolute contraindication to its use in the first 16 weeks of pregnancy.

Undesireable effects: Events suc as euphoria, disorientation, sedation, nausea, vomiting, dizziness and genralised tingling are commonly described. These events are generally minor and rapidly reversible. Prolonged or frequent use of nitrous oxide may result in bowel distension, middle ear damage and rupture of ear drums, megaloblastic anaemia, agranulocytosis, myeloneuropathy and sub-acute combined degenration.

Overdose: when used appropriately there is no risk of overdose with ENTONOX®. Inappropriate, unwitting or deliberate inhalation of ENTONOX® will ultimately result in unconsciousness, pass through stages of increasing light headednessand intoxication. The treatment is removal to fresh air, mouth to mouth resuscitation and, if necessary, the use of an oxygen resuscitator.

Full prescribtion information is available upon request.

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Clinical benefits of ENTONOX®:

Predictable and reliable analgesia with concious sedation

Mother remains in control during labour with a natural birth experience

Reduce patients fear and anxiety

Reduce treatment time and increase patient turnaround which lead to saving

Reduce post-intervention monitoring

Speedy reversal of effects when required

Do not mask signs and symptoms that may later be necessary for definitive diagnosis of the injury or illnes

Can be used by kidney and liver patients

Can be used safely by other healthcare workers (nurses, ambulance staffs etc) who have been trained in its use and are able to offer it to patients for self-administration

Mechanism of delivery is non-invasive, simple-to-use, patient-controlled, self-administered and on-deman basis

Individualize dosage for pain relief; according to the paitent's pain tolerance

Inhalation stops when patients feel drowsy because the face mask or mouthpiece will drop off

Cost-effective alternative for pain relief

High patient acceptence

The unique features of ENTONOX® allows it to be given to patients on demand basis when pin connot be tolerated once the procedure has begun; instead of stopping the procedure and waiting for arrival of a doctor to prescribe analgesic or waiting analgesic to take effect