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Nitrous oxide—an outdated anaesthetic

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When the pain-reducing properties of nitrous oxide were recognized and it was first used intentionally to cut off the perception of pain, Horace Wells exclaimed: 'It is the greatest discovery ever made! I didn't feel it so much as the prick of a pin'.[1] This was the hour of the birth of anaesthesia and the starting point of one of the most remarkable developments in medicine ever.

Thus, nitrous oxide has for many decades been an indispensable component of the standard anaesthetic breathing gas and consequently of modern general anaesthesia. However, with the end of the 20th century its zenith had been left far behind. The evolution of anaesthetic agents and research in this field have led to the development of new volatile and intravenous anaesthetics with improved clinical effects and properties, resulting in the possibility that nitrous oxide might be abandoned—notably in low-flow techniques. At the same time the recognition of possible adverse effects of nitrous oxide have increased remarkably, and as a result the usefulness of nitrous oxide as a basic component of general anaesthesia and an important carrier gas has steadily become more and more limited with each passing year.

CLINICAL CONSIDERATIONS

Many negative characteristics—well known for years—have in any case limited the use of nitrous oxide in certain clinical settings. These limitations were mainly to due its physical property of diffusing into any physiologically and pathologically air-filled compartment, leading to an accumulation of nitrous oxide and a consequent increase in hydrostatic pressure in these spaces. Nitrous oxide has therefore always been contraindicated in any clinical setting involving air accumulation, as with pneumothorax,

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pneumoencephalon, pneumopericardium, bowel obstruction, or any procedure associated with intracorporeal air enclosure such as middle ear surgery, ophthalmo-surgery, and in all cases with an increased risk of air embolism.[2–5] The diffusion properties of nitric oxide may especially cause problems in neonates suffering from gastroschisis, omphalocoel or enterothorax. Even closure of the abdominal wall may be more difficult when nitric oxide is used for anaesthesia. Many surgeons therefore blame nitrous oxide for impairing their operating conditions. Postoperative recovery of bowel function is delayed and hospital stay is prolonged.[6] Although there is some evidence in the literature to put this view into perspective, the use of nitrous oxide in visceral surgery is regarded as contraindicated in many hospitals.[7,8]

In adults, nitrous oxide increases cerebral blood flow, increases cerebral metabolic rate of oxygen, reduces cerebral autoregulation, and may increase intracranial pressure.[9,10] In children, data vary concerning middle cerebral artery blood flow and cerebral vasoreactivity depending on the type and concentration of volatile or intravenous anaesthetics used.[11–15]

It is well known that nitrous oxide scarcely affects the cardiovascular system in the healthy adult and infant and thus is considered to be non-cardiodepressive. This has recently been confirmed again by new clinical and experimental investigations.[16–18]

The haemodynamic stability which is preserved by nitrous oxide may be attributed to a compensatory result of the negative inotropic effect caused by inhibition of cytochrome *C* oxidase on the one hand and a stimulation of the sympathetic nervous system on the other. Nitrous oxide does not seem to influence coronary perfusion. An experimental study in dogs demonstrated that it did not influence coronary vascular tone or myocardial blood flow.[19]

Several experimental studies in animals show that nitrous oxide leads to a vasoconstriction in the systemic and especially the pulmonary circulation, putatively by an α-adrenergic mechanism which may result in pulmonary vasoconstriction and consequently in an increase in pulmonary vascular resistance and pulmonary artery pressure.[20,21] Thus the use of nitrous oxide in patients with pre-existing elevated pulmonary vascular resistance may aggravate pulmonary hypertension and result in right ventricular pressure overload.[22] In patients with impaired systemic circulation the use of nitrous oxide may also be associated with problems. It is known from patients with markedly reduced left ventricular function or increased activation of the sympathetic nervous system that its negative inotropic effects predominate here.[23–26] As a consequence, nitrous oxide should not be used in patients with any cardiovascular risk profile or any underlying cardiovascular disease associated with elevated vascular resistance and reduced cardiac performance, or it should at least be used with great caution.

Nitrous oxide increases the respiratory frequency and the tidal volume is reduced in the spontaneous breathing patient. While the ventilation is kept almost constant, a relevant concern is that nitrous oxide—even at low concentrations—may attenuate the so-called 'hypoxic drive', the respiratory response to a hypoxic stimulus, which is mediated by chemoreceptors. Loss of reactivity to the hypoxic stimulus, however, is very significant for the stay in the recovery room where the patient may be endangered by hypoxic phases, another potential source of harm to the patient caused by nitrous oxide.[27]

Nitrous oxide is also a cause of postoperative nausea and vomiting. Meta-analyses of numerous studies have shown that nitrous oxide significantly increases postoperative vomiting, albeit its influence on postoperative nausea may be of minor relevance. However, the postoperative nausea aspect remains controversial in the literature.[28–30]