Use of nitrous oxide in anaesthesia

Editor—Enlund and colleagues\(^1\) reported stopping the routine use of \(\text{N}_2\text{O}\) in their department. Some of their theoretical considerations and their rhetorical question ‘has the value of \(\text{N}_2\text{O}\) been overestimated?’ are begging for comment.

In 1990, Eger and colleagues\(^2\) found in an empirical study, that omission of \(\text{N}_2\text{O}\) increased isoflurane requirements only marginally—from an average of 0.64% with \(\text{N}_2\text{O}\) 60% to 0.85% without. The value of \(\text{N}_2\text{O}\) added to a halogenated vapour, is usually thought of in terms of ‘MAC reduction’ of that vapour. Therefore, Enlund and colleagues anticipated that for every 10% \(\text{N}_2\text{O}\), the concentration of vapour could be reduced by 0.1 MAC.\(^3\) Based on reported MAC values, this would amount to isoflurane 0.7% for \(\text{N}_2\text{O}\) 60%. This fallacy has plagued the anaesthetic community ever since the introduction of the MAC concept.\(^3\)

Not that anything is wrong with MAC in itself—it measures what it purports to measure: the potency of an inhaled anaesthetic to cause absence of a motor response following a noxious stimulus. The fallacy is in equating this with ‘anaesthetic potency’, since anaesthesia is not a single entity. Anaesthesia is a spectrum of effects on many different neuronal, functional and anatomical substrates. The most important of these effects are, for practical purposes, ‘unconsciousness’ and amnesia, both probably a spectrum of physiological effects. (Immobility, whilst useful, can be achieved by ancillary drugs.) Each of these effects has its own dose–response curve, with its own shape, slope, and EC\(_{50}\). MAC only represents the EC\(_{50}\) for the endpoint of immobility after noxious stimulation. There is nothing to suggest that the ratio between potency to cause immobility and potency to cause unconsciousness is the same for all agents—but this has been assumed for decades, despite evidence to the contrary. A study from the department where MAC originated clearly demonstrated that \(\text{N}_2\text{O}\) is less potent in causing unconsciousness and amnesia than isoflurane at equal MAC fractions. At 0.45 MAC isoflurane, less than 10% of volunteers responded to verbal command, whilst at 0.45 MAC \(\text{N}_2\text{O}\) all volunteers responded. Conscious memory was prevented by 0.45 MAC isoflurane, but not completely prevented by even 0.6 MAC \(\text{N}_2\text{O}\) (the highest concentration tested). A modelled EC\(_{50}\) for prevention of conscious memory was 0.2 MAC for isoflurane (95% confidence interval 0.14–0.27), and 0.5 MAC for \(\text{N}_2\text{O}\) (0.43–0.55).\(^4\) In effect, \(\text{N}_2\text{O}\) is less than half as potent an amnesic and hypnotic than was implicitly extrapolated from its potency as an immobilizer. To a lesser degree, this is also true for other agents. For example, halothane is a less potent hypnotic than isoflurane at equal MAC fractions. According to Eger, MAC\(_{\text{awake}}\) of halothane is 0.65 MAC, and that of isoflurane is 0.34 MAC.\(^5\)

It should come as no surprise that the EC\(_{50}\) for one effect does not allow extrapolation to other effects, since different phenomena are mediated by different neuroanatomical and functional substrates. Movement in response to a noxious stimulus is largely mediated by the spinal cord.\(^6,7\) Hypnosis and amnesia are largely not. It is well known that any given anaesthetic agent produces a heterogeneous pattern of depression of various areas of the central nervous system, and that these patterns vary between agents.\(^8,9\)

A further possible fallacy is the tacit assumption that the hypnotic effect of \(\text{N}_2\text{O}\) (small as it is) would be additive to that of a co-administered halogenated vapour. A volunteer study suggested a subadditive effect/partial antagonism on memory suppression.\(^10\) Using the EEG median frequency as an endpoint, however, Röpcke and Schwilden claimed additivity, with each 10% of \(\text{N}_2\text{O}\) replacing 0.04% of isoflurane (i.e. approximately a third of its effect on MAC).\(^11\) My interpretation of their data is that they support linearity, but allow no conclusion of additivity. Other authors\(^12\) have found EEG activation with \(\text{N}_2\text{O}\), which would suggest a (partially) antagonistic action.

In summary, the ‘vapour sparing’ effect of \(\text{N}_2\text{O}\) for the endpoints of unconsciousness and amnesia is small, at best in the region of isoflurane 0.3% for \(\text{N}_2\text{O}\) 70%, based on findings of the above quoted studies. Whether this reduction in vapour requirement represents any benefit for the patient, has never been substantiated. I suspect such belief is an atavism from times when anaesthetists worked with chloroform, trichloroethylene, and halothane.

I congratulate Enlund, Edmark, and Revenäö and their whole department on their decision to abandon the routine use of \(\text{N}_2\text{O}\) three years ago. They might be bemused to hear that at the same time, their colleagues in the UK spent millions of pounds on upgrading their equipment to prevent the administration of hypoxic mixtures of \(\text{N}_2\text{O}\).

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Editor—We welcome and appreciate the comments from Dr Dimpel. His comprehensive survey is an elegant summary of the pharmacodynamic shortcomings of \(\text{N}_2\text{O}\). Dr Dimpel has filled the vacuum left by the limited number of references allowed in the Short Communication format. The list of references supporting the relative impotency of \(\text{N}_2\text{O}\) could be even longer. For instance, Badner and colleagues\(^13\) found the same magnitude of difference in required isoflurane concentration, 0.19%, when used with \(\text{O}_2\) in air or \(\text{O}_2\) and \(\text{N}_2\text{O}\).

This reference also serves as a good example of a potentially serious, but surprisingly neglected, side-effect of \(\text{N}_2\text{O}\). It was clearly shown that \(\text{N}_2\text{O}\) releases homocysteine into plasma.\(^13\) The homocysteine release seems to be more than a surrogate marker for myocardial ischaemia. As professionals we have to reconsider our interventions regularly. We are experts in risk-benefit calculations, but for some curious reason many anaesthetists do not reflect over the use of \(\text{N}_2\text{O}\). Over all, \(\text{N}_2\text{O}\) consumption is going down in western European countries, but the trend differs between countries, and certainly within countries (data from the Euroanaesthesia meeting in Glasgow, May 31–June 2, 2003; EAAS2, Scholz J.). Within a narrow health economic perspective, \(\text{N}_2\text{O}\) seems to be cost-efficient (i.e. the drug acquisition cost is low). When considering costs for installation and maintenance of pipes, valves and pressure regulators; the costs of the long list of side-effects; and add its minimal hypnotic sparing effect, then we come to the obvious conclusion: omit the routine use of \(\text{N}_2\text{O}\).

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