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CLINICAL INVESTIGATIONS

Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man[†]

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Background. The motivation for this study was the current difficulty in estimating the total age-related MAC for a patient in a clinical setting.

Methods. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane were developed for the clinically useful MAC range (0.6–1.6), age range 5–95 yr, and put in a convenient form for use by practising anaesthetists. The charts are based on Mapleson's meta-analysis (1996) of the available MAC data and can be used to allow for the contribution of nitrous oxide to the total MAC.

Results. The charts indicate the influence of age on anaesthetic requirements, showing, for example, that a total MAC of 1.2 using isoflurane and nitrous oxide 67% in oxygen requires an end-expired isoflurane concentration of only 0.25% in a patient of 95 yr *vs* 1% in a 5-yr-old patient. Colleagues found the charts to be helpful and simple to use clinically.

Conclusions. The iso-MAC charts show clearly how patient age can be used to guide the choice of end-expired agent concentration. They also allow a consistent total MAC to be maintained when changing the inspired nitrous oxide concentration, thereby reducing the chance of inadvertent awareness, particularly at the extremes of age.

It has long been known that MAC, the minimum alveolar concentration at 1 atmosphere that prevents movement in 50% of patients exposed to a surgical incision,[1–3] decreases with age.[1 4] In 1996, Mapleson[5] reported a meta-analysis of the available data (Table 1) and found that (i) semi-logarithmic plots of MAC against age (age ⩾1 yr) for all inhalational agents are linear and parallel, and (ii) the available data can be represented by an equation,

$$\mathrm{MAC}_{age} = \mathrm{MAC}_{40} \times 10^{-0.00269(\mathrm{age}-40)} \qquad (1)$$

which expresses MAC for a given age (MAC_{age}) as a function of that at 40 yr (MAC_{40}). It is noteworthy that the more recent MAC data of Fragen and Dunn,[6] Nakahara and colleagues[7] and Eger[8] are in accord with the Mapleson data.

However, as a nitrous oxide–oxygen mixture is used in the majority of anaesthetics, it was felt that a simple chart

that allows for the presence of nitrous oxide and is convenient to use would be a useful guide, particularly when anaesthetizing patients at the extremes of age. Mapleson's Equation 1 (see above)[5] was used as the basis for developing a series of age-related iso-MAC charts for clinical use, the motivation being the lack of an age-related MAC display on anaesthesia monitors.

Methods

When a volatile anaesthetic is administered at an end-expired concentration ($F\mathrm{E}'$) in oxygen, this can be described as a multiple (or submultiple) k of MAC:

$$F\mathrm{E}' = k \times \mathrm{MAC}_{age} \qquad (2)$$

[†]This article is accompanied by the Editorial.

To show how F_E' varies with age for any given value of k, Equation 1 was substituted in Equation 2:

$$F_E' = k \times MAC_{40} \times 10^{-0.00269(age-40)} \qquad (3)$$

Equation 3 was then used to plot graphs of F_E' against age for a range of MAC multiples: 0.6–1.6 in steps of 0.2. This covers the range most likely to be used in clinical practice, the lower value being similar to that being used increasingly to supplement remifentanil infusions.[9–11] Because the charts are for clinical use, the F_E' scale was made linear rather than logarithmic.[5]

Additional scales for F_E' when the volatile anaesthetic is carried in nitrous oxide 50% or 67% in oxygen were included in the graph (see Appendix). These scales were shown on additional ordinates. The charts were generated using mathsPIC,[12–14] as this allows the accurate placement of additional non-standard axes. The charts were tested by colleagues for practicality in clinical use.

Results

Iso-MAC charts for the inhalational agents isoflurane, sevoflurane and desflurane are shown in Figs 1–3. Dots on the curves are to help alignment with age. The ordinates (left and right) are scaled as end-expired agent concentration (%) and the abscissa is scaled as years of age. The left-hand scale is for use with oxygen 100%; the two right-hand scales are for use with nitrous oxide 50 and 67% in oxygen.

To illustrate the use of the charts, consider an 85-yr-old patient for whom the end-expired concentrations of sevoflurane and nitrous oxide are 0.5 and 67% respectively. To determine the total age-related MAC, use the sevoflurane chart (Fig. 2) and first draw a vertical line corresponding to age 85 yr. Next, select the right-hand scale corresponding to the use of nitrous oxide 67%, and draw a horizontal line through the sevoflurane 0.5% position. The two lines intersect on the 1.2 iso-MAC curve.

This result can be confirmed by calculation. The total age-related MAC is the sum of the MAC fractions for each inhalational agent, where the MAC fraction for a given agent is $F_E'_{agent} / MAC_{age,agent}$ and is given by Equation 2. The total MAC_{85} is therefore given by

$$\text{total } MAC_{85} = \frac{F_E'_{sevoflurane}}{MAC_{85,\,sevoflurane}} + \frac{F_E'_{N_2O}}{MAC_{85,\,N_2O}}$$

$$= \frac{0.5}{1.8 \times 10^{-0.00269(85-40)}} + \frac{67}{104 \times 10^{-0.00269(85-40)}}$$

$$= 0.367 + 0.847$$

$$= 1.21$$

The charts can also be used in reverse. Suppose it is required to achieve a MAC of 1.2 in a 25-yr-old using isoflurane in nitrous oxide 50%. In Fig. 1, draw a vertical line through the age 25 position and note where it cuts the 1.2 iso-MAC curve. Follow the horizontal broken line to the

Table 1 MAC data based on age ≥1 yr. The 95% confidence limits (CL) for ages 1 and 80 yr are up to 1% greater than at MAC_{40} (from Mapleson)[5]

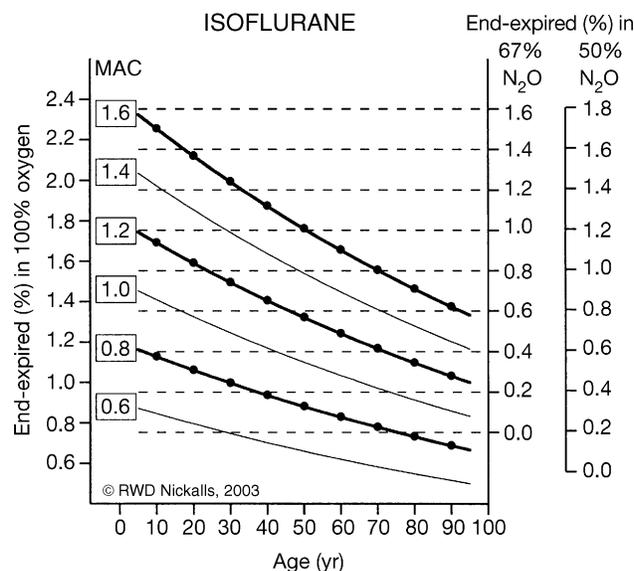| Agent	Age			95% CL ($\pm$ % MAC_{40})
	1 yr	40 yr	80 yr	
Halothane	0.95	0.75	0.58	6
Isoflurane	1.49	1.17	0.91	6
Enflurane	2.08	1.63	1.27	17
Sevoflurane	2.29	1.80	1.40	6
Desflurane	8.3	6.6	5.1	10
Xenon	92	72	57	16
Nitrous oxide	133	104	81	8

Fig 1 Iso-MAC chart for isoflurane (age ≥1 yr). The iso-MAC curves are drawn for MAC (0.6–1.6) using Equation 3 (adapted from Mapleson).[5] The dots on the iso-MAC curves are to help alignment. The left-hand ordinate scale indicates the end-expired isoflurane concentration when using oxygen 100%. The two right-hand ordinate scales indicate the end-expired isoflurane concentration when using nitrous oxide 50 and 67% in oxygen. The vertical shifts for the nitrous oxide 50 and 67% scales are 0.56 and 0.75 respectively (see Appendix). For a given age and MAC, the associated end-expired isoflurane concentration is read from the appropriate ordinate scale. For example, a MAC of 1.2 for a 60-yr-old patient using isoflurane and nitrous oxide 67% in oxygen requires an end-expired isoflurane concentration of ~0.5%.

right-hand ordinate associated with nitrous oxide 50% and read the end-expired isoflurane concentration: ~1.0%.

Colleagues found the charts to be helpful and simple to use clinically. An electronic form of the iso-MAC charts giving a real-time digital output of age-related total MAC has been used uneventfully since 1997 as part of an automated anaesthesia information system developed by one of the authors (RWDN).

Discussion

The iso-MAC charts have been designed to make it easy for the depth of anaesthesia to be determined in MAC units
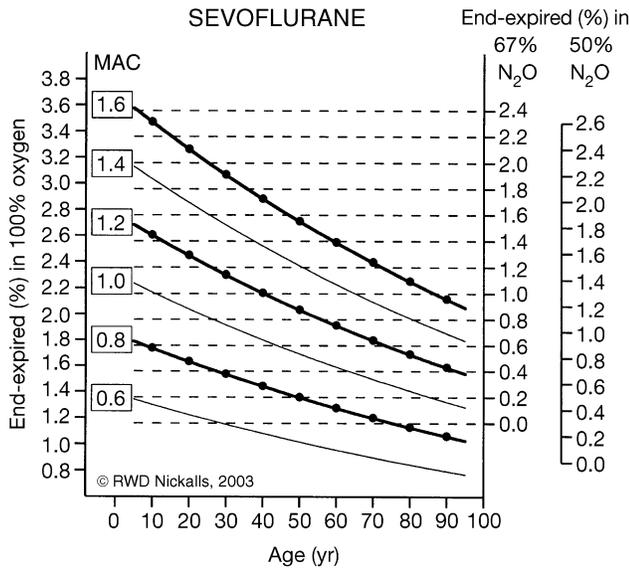
Fig 2 Iso-MAC chart for sevoflurane (age ⩾1 yr). The vertical shifts for the nitrous oxide 50 and 67% scales are 0.86 and 1.16 respectively (see Fig. 1 legend for details and interpretation).
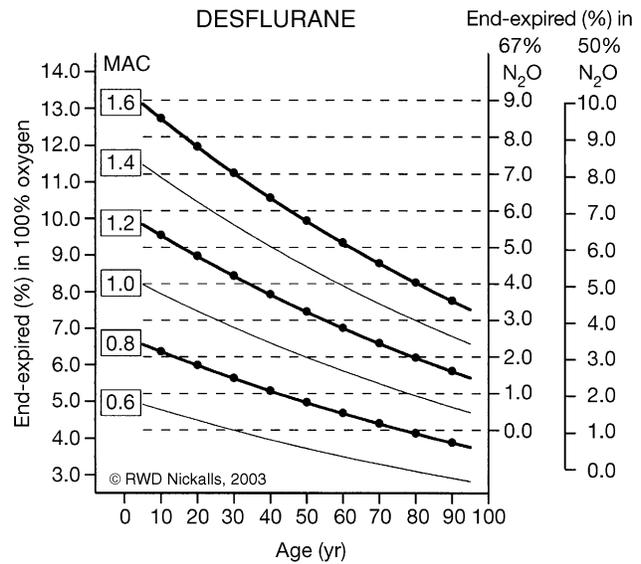
Fig 3 Iso-MAC chart for desflurane (age ⩾1 yr) The vertical shifts for the nitrous oxide 50 and 67% scales are 3.15 and 4.22 respectively (see Fig. 1 legend for details and interpretation).

when using volatile agents, not only in oxygen 100% but also in conjunction with two commonly used concentrations of nitrous oxide, and for a wide range of ages. It is envisaged that these charts will be updated periodically as more MAC data become available.

More specifically, the practical value of the iso-MAC charts is twofold. First, they show clearly and easily how patient age can be used to guide the choice of end-expired agent concentration when it is carried in pure oxygen (or an oxygen–air mixture) or in nitrous oxide 50 or 67% in oxygen. Secondly, they allow a consistent total MAC to be maintained when making changes to the fractional inspired nitrous oxide concentration ($F_{I_{N_2O}}$).

To make the iso-MAC charts usable in the presence of nitrous oxide, it was necessary to invoke the generally accepted principle that the clinical effects of the inhalational agents in current use are additive.[5–8 15–19] While additivity has not been proved conclusively, it is the best working hypothesis. A significant body of the literature is consistent with this hypothesis, and no human data contradict it.

As the variation of MAC with age is often underestimated by clinicians, the iso-MAC charts are particularly useful when dealing with patients at the extremes of age. For example, Fig. 1 shows that a total MAC of 1.2 using isoflurane and nitrous oxide 67% in oxygen requires an end-expired isoflurane concentration of only 0.25% in a patient of 95 yr *vs* 1% in a 5-yr-old patient. This very large difference exists partly because the nitrous oxide 67% provides a smaller fraction of MAC in the 5-yr-old (52 against 91%).

Sometimes it is necessary for surgical reasons to reduce the $F_{I_{N_2O}}$ or even to stop using nitrous oxide altogether (e.g. in ear or bowel surgery), in which case the iso-MAC chart

serves as a useful guide to the required increase in the end-expired concentration of the volatile agent necessary to maintain a consistent total MAC. For example, in order to maintain a total MAC of 1.2 in an 80-yr-old patient using desflurane and nitrous oxide 67% in oxygen, it is clear from Fig. 3 that an increase in the $F_{I_{O_2}}$ from 33 to 100%, associated with eliminating nitrous oxide, requires a compensatory three-fold increase in the end-expired concentration of desflurane, from 2 to 6.25%. However, in this setting (i.e. decreasing the $F_{I_{N_2O}}$ and increasing the inspired concentration of the volatile agent) it is important to appreciate that the greater solubility of the volatile agent in the tissues,[20] particularly for sevoflurane and isoflurane, means that the increase in the arterial and brain concentrations of the volatile agent towards equilibrium with the reset end-expired concentration will be slower than the corresponding decline in the end-expired concentration of nitrous oxide.[1] Therefore, despite the three-fold increase in end-expired desflurane, there is likely to be temporary lightening of the depth of anaesthesia unless an even greater concentration of desflurane was used for a few minutes.

As the charts make it easy to determine age-related MAC in a clinical setting when using the commonly used inhalational agents, they have the potential for reducing the chance of inadvertent awareness, particularly at the extremes of age.

Appendix

If the end-expired concentration of any one agent i is expressed as a multiple (or submultiple) k_i of the relevant value of MAC, then

$$\frac{F_{E'_i}}{MAC_{age,\,i}} = k_i \qquad (4)$$

On the basis of the increasingly accepted view that the effects of the inhalational anaesthetic agents are additive in man,[5–8 15–19] it follows that the total MAC multiple of two inhalational anaesthetics given together is the sum of the individual MAC multiples. Therefore, when a volatile anaesthetic agent is used with nitrous oxide in oxygen

$$k_{total} = k_{volatile} + k_{N_2O} \qquad (5)$$

Therefore, substituting Equation 4, for both the volatile and the nitrous oxide, in Equation 5 and writing $F_{E'_{volatile+}}$ for the end-expired concentration of the volatile agent when given with nitrous oxide gives

$$k_{total} = \frac{F_{E'_{volatile+}}}{MAC_{age,\,volatile}} + \frac{F_{E'_{N_2O}}}{MAC_{age,\,N_2O}} \qquad (6)$$

To find the end-expired concentration of volatile agent needed for a given total MAC multiple in the presence of a given end-expired concentration of nitrous oxide, Equation 6 can be rearranged to give

$$F_{E'_{volatile+}} = k_{total} \times MAC_{age,\,volatile}$$
$$- \left\{ F_{E'_{N_2O}} \times \frac{MAC_{age,\,volatile}}{MAC_{age,\,N_2O}} \right\} \qquad (7)$$

To achieve the same k_{total} with the volatile agent in oxygen 100% requires an end-expired concentration $F_{E'_{volatile}}$ which is given by

$$F_{E'_{volatile}} = k_{total} \times MAC_{age,\,volatile} \qquad (8)$$

Combining Equations 7 and 8 shows that

$$F_{E'_{volatile+}} = F_{E'_{volatile}}$$
$$- \left\{ F_{E'_{N_2O}} \times \frac{MAC_{age,\,volatile}}{MAC_{age,\,N_2O}} \right\} \qquad (9)$$

The finding[5] that the regression lines of log(MAC) for the different anaesthetics are parallel implies that the ratio $MAC_{age,volatile}$ / MAC_{age,N_2O} is the same for all ages, e.g. 1.49/133=0.01120, 1.17/104=0.01125 and 0.91/81=0.01123 for isoflurane at 1, 40 and 80 yr respectively, rounding errors in the MAC values in Table 1 accounting for the slight variation between ages. Therefore, with isoflurane, for instance, and using the mean (0.01123) of the three values for the ratio, if a given MAC multiple requires a particular

$F_{E'_{isoflurane}}$ in oxygen 100%, the required $F_{E'_{isoflurane+}}$ with nitrous oxide 50% in oxygen will be 50×0.01123=0.56% *less* than when using 100% oxygen. Accordingly, an $F_{E'}$ scale for isoflurane with nitrous oxide 50% in oxygen will simply be shifted 0.56% compared with that for the scale for use with 100% oxygen. With nitrous oxide 67% the shift is 0.75%. Corresponding shifts are 0.86 and 1.16% for sevoflurane, and 3.15 and 4.22% for desflurane.

Acknowledgement

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