MANAGEMENT OF CARBOXYHAEMOGLOBINAEsIA

Sir,—Drs Vegfors and Lennmarken have demonstrated usefully how easy it is to be misled in the management of carbon monoxide poisoning [1]. Their case deserves further comment.

Unfortunately, there is little information on the mechanism of cellular toxicity of carbon monoxide. Carbon monoxide binds to haem-containing enzymes such as cytochrome P450 [2]. Measurements of carboxyhaemoglobin concentration are not helpful in determining the degree of tissue poisoning [3]. In particular, the likelihood of late neuropsychiatric problems, such as memory disturbance, is difficult to predict [4]. Up to 43% of survivors may have such sequelae if followed up for 3 years [5].

Vegfors and Lennmarken suggested that an elimination half-life of 2 h was sufficient. As they point out, the use of 100% oxygen at ambient pressure and at 3 atm abs would have reduced this to 1 h and to 20 min, respectively. Intracellular concentrations of carbon monoxide cannot be measured at present, but it is assumed that oxygen therapy similarly increases the elimination from the tissues and so reduces tissue damage.

Hyperbaric oxygen appears to reduce both acute symptoms and neuropsychiatric complications [2]; however, its exact role has yet to be determined. Members of the British Isles Group of Hyperbaric Therapists are planning a prospective controlled study which will look at this issue—particularly regarding long-term morbidity. In the meantime, every case of suspected carbon monoxide poisoning should be treated with 100% oxygen. Patients with evidence of severe poisoning should be referred for hyperbaric oxygen [6]. This Hyperbaric Unit will consider a patient who has any one of the following: loss of consciousness at any stage since exposure to carbon monoxide; neuropsychological symptoms other than a mild headache; cardiac complications, including ischaemia and arrhythmias; carboxyhaemoglobin concentration greater than 20%, at any time; pregnancy.

This Hyperbaric Unit may be contacted via the Duty Consultant, Intensive Therapy Unit, Whips Cross Hospital (Tel.: 081 539 5522). Other Hyperbaric Units may be contacted via the British Isles Group of Hyperbaric Therapists, Diving Diseases Research Centre, Fort Bovisand, Plymouth (Tel.: 0752 408093).

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REFERENCES
The significance of the supramaximal stimulus is ill defined; it may be considered to be the stimulus required so that no further recruitment of muscle fibres occurs. There are no known determinants of the supramaximal stimulus, although it has been suggested that accuracy of electrode placement and variable output from stimulators may influence the current. Transmitter–receptor interactions should influence the current evoking a supramaximal stimulus. Anticholinesterase therapy is associated with increased leakage of transmitter, thus decreasing the amount per evoked stimulus. Additionally, the nerve relies on choline derived by depolarizing nerve endings [3]. It is highly likely that those being pretreated with pyridostigmine will have less Ach available for release on stimulation with an increasing intensity of current.

The supramaximal stimulus is one of the variables used most frequently in neuromuscular junction studies and its determinants need elucidating. It is hoped that this small study will serve as a stimulus to further investigation.

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ANALYSIS OF EFFECTS OF DRUG COMBINATIONS
Sir,—Administration of multiple drugs having similar effects is common in anaesthesia, and so there is a great need for articles such as that by Naguib and Sari-Kouzel [1] and the accompanying editorial [2], which further our understanding of the actions of drug combinations. It was stated correctly [2] that the most common method of analysing drug combination data is isobolographic analysis. We wish to point out limitations of this method and the availability of an alternative approach applicable to many drugs used in anaesthesia.

Isobolograms were developed originally as a descriptive rather than an analytical tool. Several methods have been proposed for basing statistical tests on isobolograms, but the problem is complicated because all the elements (equieffective doses of the two drugs, amounts of the two drugs in the equieffective combination) are determined experimentally and hence subject to error. The only approach which we feel to be fully satisfactory [3] is limited to the case where the combination contains the two drugs in a fixed ratio, but this has not enjoyed widespread use. Naguib and Sari-Kouzel used a test to determine if the distance of the combined drug ED_{50} from the ED_{50} isobol was significantly greater than zero. This distance was measured perpendicular to the isobol, a choice which seems curious to us, as, because the combination consisted of a fixed dose of thiopentone plus varying amounts of propofol, the 95% confidence interval for the combined drug ED_{50} lies in the horizontal direction. There are very good biological reasons why actions of different drugs or their combinations may exhibit differing variability; approximation of variability in the direction perpendicular to the isobol from that parallel to the isobol by purely mathematical means is therefore likely to entail an unquantifiable error.

The isobolographic method has drawbacks other than the difficulty of statistical analysis. One isobol relates to a single effect level; conclusions may not apply at other levels. Hence, one might conduct separate analyses at the ED_{10}, ED_{25}, ED_{75}, etc. Furthermore, the compositions of the drug combinations are restricted to either a fixed ratio combination, or a fixed dose of one drug plus varying amounts of the other. An alternative method [4], applicable when both drugs have linear (log-dose)-response curves over the range of interest, does not have these limitations. In this approach, the raw data (administered drug doses and responses) are used directly, as we may consider the doses administered to be fixed and only the response to be subject to random error, the statistical problem is greatly simplified. If we have a mixture containing dose A of one drug and dose B of another, we use the relative potency, P_{i} (which may vary with dose) of the drugs to convert the dose of one of the drugs to an "equivalent" amount of the other. If drug effects are additive, response to either drug alone or their combination is then given by:

\[ \text{response} = \beta_{1} + \beta_{2} \log(A+B) \]

This approach extends the familiar concept of the dose–response curve to a mathematical model where the response depends on doses of two drugs. Additional terms may be included in the model to describe non-additive interactions of the drugs.

We have used this approach successfully to study the combinations of thiopentone and midazolam [5] and propofol and midazolam [6], and combinations of other drugs having quantal or graded responses [4]. Unfortunately, the article by Naguib and Sari-Kouzel did not include any raw data, so we are unable to demonstrate this approach with their results. We hope that the availability of this additional tool will encourage further research into the actions of drug combinations which are so common in anaesthesia.

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Sir,—Thank you for the opportunity to respond to the letter of Drs Plummer and Short which, we hope, is an isolated case of misunderstanding of the isobolographic technique. The isobolographic method is an analytical tool similar to the model described by Short, Galletly and Plummer [1]. Their present argument against the isobolographic analysis can be used also against their model, which also was fitted to experimental data [1] and is subject to error. In our report [2], the distance of the combined drug ED_{50} was measured perpendicular to the ED_{50} isobol to demonstrate the degree of deviation of the former point from the additive line. We wonder how Drs Plummer and Short would demonstrate this measurement otherwise.

We recognize that Plummer and colleagues have provided a simplistic approach for analysis of drug combinations in a model which was adapted from Finney [3]. We believe that their model