LETTERS TO THE EDITOR

Estimation of Pulmonary Shunt

Dear Sir,

I wish to comment on the recent paper of Fournier and Major (1981).[1] Firstly they have misquoted Comroe[2] in the alveolar air equation.

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \left[\frac{F_{I_{O_2}} (1 - F_{I_{O_2}})}{R} \right].$$

The correct equation is:

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \left[F_{I_{O_2}} + \frac{1 - F_{I_{O_2}}}{R} \right].$$

The equation in the paper by Fournier and Major is valid only for an $F_{I_{O_2}} = 1.0$ and $R = 1.0$. At an F less than 1.0 use of their equation will lead to considerable error in the calculation of A-a gradient.

Secondly the "Clinical Short-Cut" method of calculating makes the incredible assumption that mixed venous oxygen content ($C\bar{v}_{O_2}$) is 3.5 ml less than the arterial oxygen content (Ca_{O_2}). This assumption may be satisfactory for a patient with a normal cardiac output and normal oxygen consumption but will lead to gross errors in shunt calculation if used for patients with a low cardiac output or increased total body oxygen consumption.

I would suggest that the only reason they were able to obtain a reasonable correlation was that their patients mainly had a normal cardiac output. As an example in patient No. 17 this assumption has resulted in an error of greater than 100 per cent (29.8 per cent by "short cut" method as compared with 13.0 per cent by the more precise method).

To use their "Clinical Short Cut" method in critically ill patients would result in larger inaccuracies in shunt estimation.

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Estimation of Pulmonary Shunt (reply)

Dear Sir,

In answer to Doctor Stewart's letter, we must admit that we have misquoted Comroe's alveolar air equation. This equation is so well known that we overlooked this typographical error in our revision.

As for the considerable error introduced when the $F_{I_{O_2}}$ and the R are different than one, we must say that our patients had a $F_{I_{O_2}}$ between 0.21 and 1.0 while their respiratory quotients were measured between 0.4 and 1.0. In spite of this fact the correlation between the measured and estimated A-aDo was 0.98 which is quite acceptable.

It is evident that to use any kind of "short cut" method in clinical practice we have to make certain assumptions if we do not want to or cannot go through the long procedure. The assumption that $C\bar{v}_{O_2}$ is 3.5 ml less than arterial oxygen content (Ca_{O_2}) is not so "incredible" as it may seem. Harrison found this value to give a more representative true shunt calculation in 13 of his 15 patients who had a stable cardiovascular state. We tried this value in our critically ill patients who had an unstable cardiac output measured both by thermodilution and the Fick principle and found a correlation of 0.87 between our "short cut" method and the more precise laboratory procedure.

We do not pretend that this "short cut" method should replace the more accurate laboratory method. However we feel that this kind of calculation will enable the clinician to be in a good position to make a fairly good educated guess on the "shunt" value in his patient.

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Minaxolone

Dear Sir,

Your recent editorial entitled "Clinical Trial – the Minaxolone Story" gave the reader a somewhat one-sided account of the early clinical trials of minaxolone. This water-soluble steroid was introduced into the U.K. in November 1978 as a possible alternative to Althesin. The initial animal studies suggested that minaxolone was two

to three times as potent as Althesin,[1,2] although this was not borne out by the subsequent human studies.[3,4] However, in assessing any drug, it is important to remember that early clinical impression may not necessarily be borne out by later more extensive clinical trials. Of the favourable features of minaxolone were the absence of the solvent Cremophor EL and advantageous properties in patients with hypertension and ischaemic heart disease.[5]

Two features compared unfavourably with Althesin – the presence of excitatory movements following induction, and the prolonged recovery. Although a high incidence of excitatory movements and hypertonus were reported during induction of anaesthesia in un-premedicated patients,[4] in no patient was the severity of such responses sufficient to require intervention by the anaesthetist. Suggestions that the pronounced excitatory movements were a reflection of the epileptogenic activity seen in the Cynoolgus monkey were not substantiated in our comparative electroencephalographic studies using compressed spectral array analysis during infusions of minaxolone or Althesin.[6]

If the high incidence (40–64%) of excitatory movements[7] was to have been the sole reason for the withdrawal of the drug, then it should be remembered that similar incidences were also seen with two other clinically accepted intravenous agents, methohexitone and etomidate.[8,9,10] Premedication with opiates or diazepam, or combination with nitrous oxide, attenuated these excitatory movements in the patients receiving minaxolone.

Prolongation of recovery can be explained solely on the pharmacokinetic profile of the drug. Water-solubility will confer a different spatial volume of distribution from that of a lipophilic drug such as Althesin. Thus, although the two drugs were found to have similar terminal half-lives and plasma clearance rates, the concentrations in the various drug compartments were not identical.[6] Our data from these infusion studies of the two steroid anaesthetic agents differ from those seen after bolus doses of the drugs.[11,12] This may be attributable to the inadequate duration of sampling during the latter studies. The absence of pharmacokinetic studies in volunteers before initial clinical studies was by no means crucial. The use of subanaesthetic doses of a drug would have allowed pharmacokinetic parameters to be calculated, but could not have anticipated the observed duration of anaesthesia. Another feature, which appeared during the prolonged infusion studies was the presence of abnormal liver function tests in the post-operative period. These results were surprising in view of the absence of any cytotoxic effect during *in vitro* studies using clinically observed concentrations of the drug.[13] However, the termination of clinical trials left us without sufficient results to offer either definitive data or a satisfactory explanation for this finding.

Whether minaxolone returns for further clinical studies will obviously depend on the results of the ongoing chronic toxicity studies, and on the attitude of the drug company concerned. From the data available, there may be a place for further controlled studies of the drug, particularly for the induction and maintenance of anaesthesia in the patient with cardiac disease.

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OXYGEN ANALYSERS AS DISCONNECTION ALARM

DEAR SIR,

Re: *Use of Oxygen Analysers as a Disconnection Alarm.*

The Canadian Standards Association publication "Pulse" No. 20, May 1981 comments on the new standard for Oxygen Analysers as follows: "this device can be an effective disconnection alarm as well as an aid to regulating the oxygen level." We have considerable anxiety concerning the suggestion that an oxygen analyser should be used as a disconnection alarm.

An oxygen analyser inserted in the anaesthesia breathing circuit measures the oxygen concentration at the point in the circuit which is being monitored. A satisfactory *concentration* at that point does not imply flow and the analyser will alarm only if the oxygen *concentration at that point* falls below a preset figure. Whether or not the oxygen concentration falls at the point being monitored, when a disconnection occurs, will depend in part on the following factors:

(a) the type of anaesthetic breathing circuit in use,

(b) the position of the analyser sensor in relation to the point of disconnection and the point of fresh gas inflow in that circuit,

(c) whether the patient is breathing spontaneously or whether ventilation is being controlled and the type of ventilator in use.

To be able to monitor whether the patient is in fact *receiving* the oxygen which is being *delivered* would require a separate system, which would have to be independent of the delivery system.

We consider that the use of an oxygen analyser in the delivery system to infer the integrity of the system is fraught with danger.

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CORRECTION

MORISON, D.H., – A double-blind comparison of carbonated lidocaine and lidocaine hydrochloride in epidural anaesthesia. Can. Anaesth. Soc. Jour. *28*: 387 (July 1981)

Page 387, 5th line from the end of the "Methods" section should read –

with an α error of *0.05* and a β error of 0.1