CORRESPONDENCE

COMPARISON OF PRESSURES MEASURED FROM THE PROXIMAL EXTERNAL JUGULAR VEIN AND FROM A CENTRAL VEIN

Sir,—The study by Shah, Swai and Latto (1986) comparing the venous pressures measured from the proximal external jugular vein and from a central vein was interesting. The authors found a mean difference in pressure of 3 mm Hg from the two sites which was not influenced by alterations in the head position or the side of jugular venous catheterization.

Whether the reference zero is the right atrium or manubriosternal joint, the manometer scale or transducer must bear a constant relation to the zero (Lawler, 1980). The scale or transducer should be fixed to the patient or the operating table, rather than to a freestanding pole. The authors have failed to mention the position of the transducer in relation to the zero point. As the measurements were taken in the horizontal position, one is compelled to believe that the transducer was at the body level. Although a source of error did exist, it was probably equal for all the measurements. As long as the body position is horizontal, the measurement from a slightly distant vein like proximal external jugular may reflect near true venous pressures, as the authors have found. This is not necessarily true if the patient is tilted or slightly head-up on the operating table or intensive care bed. Then the position of the transducer becomes more important. Moreover, changes in the central venous pressure are more important than a single value, particularly after fluid challenge.

It remains to be seen what the effects of posture and fluid challenge would be on the pressures measured from the proximal external jugular vein and a central vein.

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REFERENCES


Sir,—We would like to thank Dr Kumar for his interest in our study and for his comments related to it.

We used the manubriosternal joint as the reference zero, with the transducer fixed to a free standing pole. The patient was at the same horizontal level and the transducer had a constant relationship to the reference zero throughout the study period. As the title suggests, our study compared the pressures from the external jugular vein and from a reliably placed central venous line using this reference zero. We therefore fail to understand his contention that a source of error did exist in our measurements.

We are entirely in agreement with his observation that pressures from the external jugular vein will be influenced by patient position. If the patient is placed in the head-up or head-down position, an allowance will need to be made for the hydrostatic pressure difference between the reference zero and the tip of the catheter in the external jugular vein. Indeed, adjustments may need to be made to central venous pressure measurements with changes in the patient’s position if the reference zero is the manubriosternal joint.

Measurement of the external jugular venous pressures and central venous pressure in response to a fluid challenge or changes in blood volume were not formally investigated in our cardiac patients, for obvious clinical reasons. However, the measurements in our study correlated over a wide range of pressures. Also the pressures from the two catheters during the course of cardiac anaesthesia were similar when measured.

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IN VITRO DEGRADATION OF ATRACURIUM IN HUMAN PLASMA

Sir,—The experiments reported by Stiller, Cook and Chakravorti (1985) confirm our earliest conclusions (Coker et al., 1981; Stenlake et al., 1981) that the particular structural features of atracurium enable the mutual promotion of Hofmann elimination and enzymic ester hydrolysis, in which the ester carbonyl groups facilitate Hofmann degradation and the quaternary ammonium groups enhance ester hydrolysis.

Thus, we observed about 70% decrease in potency in cats given atracurium which had been incubated for 30 min at 37 °C in pH 7.4 buffer, compared with unincubated atracurium in water acidified to pH 3.0. This finding was supported by the, as then, unpublished work of Merrett, Thompson and Webb (1983) in which potency measurements in mice, following incubation of atracurium with appropriate buffers, showed that it undergoes a non-enzymic decomposition four times faster at pH 7.6 and 10 times faster at pH 8.0 than at pH 6.9.

Such sensitivity to decomposition at mildly alkaline pH is uncharacteristic of chemically-mediated ester hydrolysis, but typical of Hofmann elimination. Accordingly, as we commented at the time, the extensive breakdown of atracurium in buffer at pH 7.4 (70%, in 30 min) rightly contrasts sharply with that of suxamethonium, which is incapable of Hofmann elimination and only 6% hydrolysed in 1 h in buffer at that pH, and no more than 12% hydrolysed in the same time at pH 7.7 (Goedde, Held and Atland, 1968). For this reason, whilst none of these experiments or the other supporting experiments reported in the same paper and elsewhere (Hughes and Chapple, 1981) distinguish unequivocally between the two breakdown reactions, we hold firmly to the view that Hofmann elimination is the predominant factor in the underlying chemical breakdown of atracurium in vitro.

We also found that atracurium was less stable in human plasma than in buffer—an observation supported by the later
work of Merrett, Thompson and Webb (1983) which showed that the rate of decomposition in human plasma was twice as rapid as that in buffer at the same pH. We concluded that this was the result of an enzyme-catalysed hydrolysis, but went on to show, by comparison with other atracurium-related compounds, that degradation was also dependent on the integrity of the Hofmann capability (Stenlake et al., 1981, table IV). This is especially relevant, as two of the primary breakdown products (quaternary alcohol and quaternary monoacrylate) are themselves capable of further degradation by both Hofmann elimination and ester hydrolysis. It is also relevant that the esterase mechanism for atracurium, in contrast to that for suxamethonium, is not dependent on pseudocholinesterase activity, and it is significant that throughout its extensive clinical use there have been no reports on atracurium of the prolonged paralysis and apnoea seen with suxamethonium in patients with pseudocholinesterase deficiency or with a typical plasma esterases.

We also reported and commented upon the biphasic pattern of release of $^{14}$C-laudanosine from $^{14}$C-atracurium iodide in reconstituted, pooled, dried human plasma, fresh human plasma, fresh whole blood and atypical human plasma with a 65% deficiency of pseudocholinesterase. There are differences between the present study and our own in methodology, atracurium salt, and the pH of the plasma samples used, and in the overall rates of laudanosine release. Nevertheless, the same pattern of an initial fast release of about 50% of the available laudanosine with subsequent slowing was very clearly demonstrated by us with all the above mentioned substrates. We still hold to the view expressed in our comment at the time, that "the sharp change in the slope of the curve is consistent with an initial fast Hofmann elimination of the intact ester accompanied by ester hydrolysis, with a reduction in the elimination rate as the quaternary acid is formed". This conclusion rests on accepted theoretical grounds that replacement of the powerful electron-withdrawing ester group (COOR), which is the key to activation of the Hofmann elimination in atracurium, by the significantly less powerful electron-withdrawing carboxyl (COOH) group of the quaternary acid will necessarily slow the elimination reaction. We would add, however, in the context of the present debate, that whilst there is no experimental evidence to support the view, there is every reason to suppose that the rates of ester hydrolysis of the quaternary monoacrylate and the quaternary alcohol are unlikely to be greatly different from that of atracurium itself, since all three contain the same structurally identical quaternary ammonium-ester function.

We therefore agree with the comments of Stiller, Cook and Chakravorti (1985) that the breakdown of atracurium in human plasma does not occur simply by two completely separate pathways. Furthermore, we submit, in extension of their conclusions, that the complete release of 2 molecules of laudanosine can only be rationalized on the basis of a fully integrated network of Hofmann eliminations and ester hydrolysies embracing atracurium and all its metabolites, as was clearly envisaged in our original publication (Stenlake et al., 1981, Scheme 3). For this reason we consider that the statement "we estimate that at 40 min, two thirds of atracurium is degraded by ester hydrolysis and one third by Hofmann elimination" by Dr Stiller and his colleagues is capable of misinterpretation—even more so when, from our reading of the graphical evidence presented (the precise molar ratio at 40 min is omitted from the table), significantly more than 1 mol of laudanosine (ca 1.2 mol) is released per mole of atracurium in that time.

The existence of ester degradation in measurable amounts in human plasma does not detract from the fact that the unique method of decomposition of atracurium, by Hofmann elimination, is responsible for the constant response in all pathological states including renal and hepatic failure (Ward and Neill, 1983), pseudocholinesterase deficiency (Baraka and Jaude, 1984) and in at least one case of organophosphorus poisoning (Baraka, Cava and Jaoude, 1984) where the cholinesterases are inhibited. Although, as yet, it has not been possible to quantify the relative contribution of Hofmann elimination in vitro, there is ample evidence that it plays a major role in the degradation of atracurium in man.

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REFERENCES

INFUSION OF ALFENTANIL OR PETHIDINE FOR SEDATION OF VENTILATED PATIENTS IN THE ITU
Sir,—I would like to comment on the article by Yate and colleagues published in your October 1986 issue. The authors conclude by saying that "Alfentanil at an infusion rate of 0.4–0.5 μg kg⁻¹ min⁻¹ can be used as the main agent for sedation of ventilated patients in the I.T.U." I would like to raise the following points.

It must be appreciated that one cannot apply the results obtained in this paper to all ventilated patients requiring sedation in the I.T.U. All patients studied were post-cardiac by-pass; they had received a mixture of opiates (papaveretum 15–20 mg, fentanyl 1 mg, and alfentanil infusion), prometha-