Methylparaben and propylparaben do not alter cerebral blood flow in humans

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In vitro studies suggest that the preservatives methylparaben and propylparaben included in some multidose vials of succinylcholine are the cerebral vasodilators responsible for the increases in intracranial pressure (ICP) documented after succinylcholine administration. To test this hypothesis, we measured cerebral blood flow (CBF) and cerebral blood flow velocity (CBFV) with inhaled ^{133}Xenon and transcranial Doppler respectively in healthy humans before and after the intravenous administration of methylparaben and propylparaben. We found no change in either CBF or CBFV after the paraben injections and therefore conclude that it is unlikely that the rise in ICP seen with succinylcholine is caused by cerebral arterial vasodilatation from the preservatives methylparaben and propylparaben.

Certaines études in vitro suggèrent que les préservatifs méthylparabène et propylparabène seraient les vasodilatateurs cérébraux responsables de l'augmentation de la pression intracrânienne observée après l'administration de succinylcholine provenant de certains vials multidoses. Pour vérifier cette hypothèse, nous avons mesuré le flot sanguin cérébral et la vélocité du flot sanguin cérébral à l'aide de xénon 133 et du doppler transcrânien chez l'humain normal avant et après l'administration intra-veineuse de méthylparabène et de propylparabène. N'ayant observé aucun changement de flot sanguin cérébral ou de vélocité du flot sanguin cérébral après l'injection de ces substances, nous en concluons que les préservatifs méthylparabène et propylparabène ne sont pas responsables de la vasodilatation artérielle cérébrale et de l'augmentation de la pression intracrânienne observée après l'administration de succinylcholine.

Key words
BRAIN: blood flow;
NEUROMUSCULAR RELAXANTS: succinylcholine;
PHARMACOLOGY: preservatives, methylparaben, propylparaben.

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Controversy still exists about the safety of succinylcholine in patients with reduced intracranial compliance, since it has been shown to increase intracranial pressure in both animals and humans.[1-3] Although a number of mechanisms has been postulated, a recent *in vitro* study performed in our laboratory indicated that it may be the preservatives, methylparaben and propylparaben included in some multidose vials of succinylcholine, rather than succinylcholine itself, which are the cerebral vasodilators.[4] We have further explored this hypothesis by measurement of cerebral blood flow (CBF) and cerebral blood flow velocity (CBFV) in healthy humans before and after the intravenous administration of methylparaben and propylparaben.

Methods

This study was conducted in two parts after Institutional Ethics Committee approval and obtaining written informed consent from each volunteer. In the first part, eight healthy volunteers were studied. Cerebral blood flow was determined from the average clearance of inhaled ^{133}Xe as measured by 16 external scintillation detectors, eight located over each cerebral hemisphere (Novo Diagnostics 10a Cerebrograph). Each subject received 5 mCi of ^{133}Xe through a sealed face mask. The ^{133}Xe clearance curves were assessed by non-compartmental height-over-area analysis.[5] Every measurement required approximately 15 min for completion, and this curve was integrated to 15 min instead of infinity in order to reduce the effect of the extracerebral component.[5] The initial slope index (ISI) was also derived.[5] As this is a measure of flow during the initial few minutes, we hoped to be able to detect early brief changes. Systemic blood pressure was measured every five minutes with an arm blood pressure cuff concurrent with each CBF.

TABLE Initial slope index (ISI) and global cerebral blood flow (CBF) (ml · 100 g^{-1} · min^{-1})

	ISI		*CBF*	
Subject	*Control*	*Paraben*	*Control*	*Paraben*
1	49	62	44	52
2	51	52	41	43
3	51	48	46	41
4	48	45	44	39
5	49	50	42	43
6	48	44	48	41
7	50	51	44	44
8	45	48	39	39
Mean	48.9	50.0	43.5	42.75
SD	2.0	5.6	2.8	4.2

After baseline CBF measurement, each volunteer received methylparaben 9 mg and propylparaben 1 mg together intravenously. This is the equivalent amount of preservative found in a 100 mg dose of a commercially available multidose vial of succinylcholine (Quelicin®). Sixty seconds after the paraben injection, the CBF measurement was repeated.

In the second part, another eight healthy volunteers were studied using transcranial Doppler. Two of these subjects had been studied in the first part. The probe of a Multigon® 2MHz pulsed transcranial Doppler velocimeter was placed against the skull just above the zygomatic arch. The side of the skull that gave the best middle cerebral artery (MCA) insonation was chosen and the probe's position was fixed for the duration of the study. Each subject was given the same amount of paraben as above or placebo (saline) in a randomized double-blinded fashion. With each injection, peak and mean flow velocity were determined at 0, 30, 60, 120, 180, 240, and 300 sec. Systemic blood pressure was measured every five minutes with an arm blood pressure cuff after the injection of paraben or placebo.

ANOVA for repeated measures was used for statistical analysis of both parts. A $P < 0.05$ was regarded as statistically significant.

Results

No adverse haemodynamic or neurological effects occurred from the paraben injections. Blood pressure remained unchanged throughout. The ^{133}Xe CBF results are shown in the Table. There was no change in CBF although it increased in one subject after paraben injection. There was no change in the peak or mean transcranial Doppler velocity in any subject including the subject who had an increase noted with the xenon measurement technique (Figure).

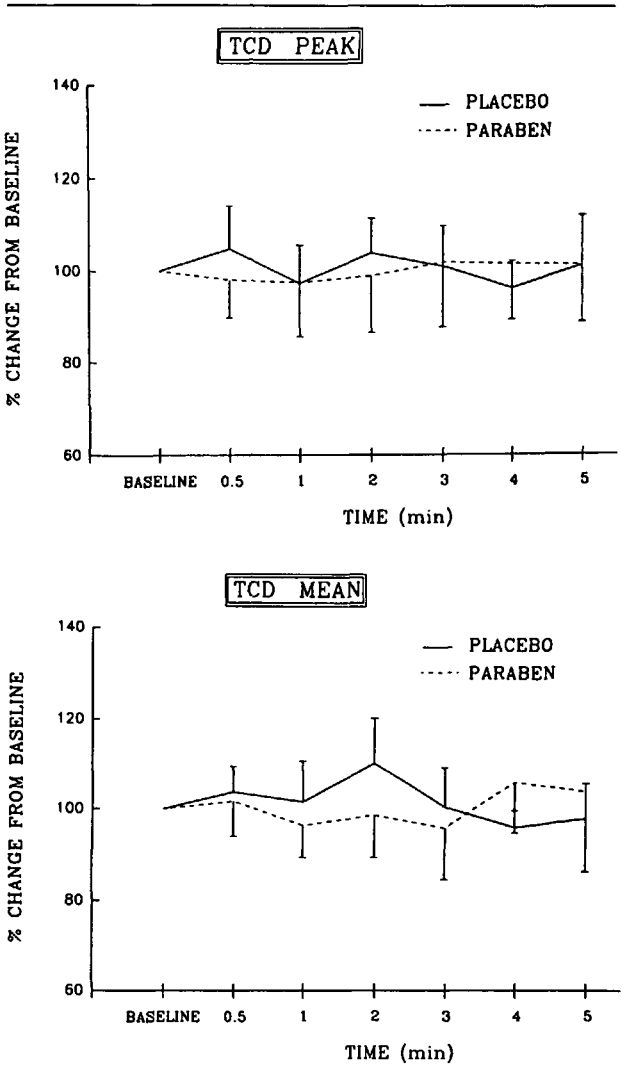

FIGURE The effects of intravenous methylparaben and propylparaben as well as saline (placebo) on peak (upper) and mean (lower) middle cerebral artery blood flow velocity. The data (mean ± SD) are expressed as a percentage of the baseline blood flow velocity.

Discussion

This study represents a continuation of our investigation of the contribution of the preservatives methylparaben and propylparaben to the cerebrovascular effects ascribed to succinylcholine. Hamilton *et al.* showed that methylparaben and propylparaben were the cause of considerable relaxation in isolated cerebral vessels treated with Quelicin®.[4] Preservative free succinylcholine, in contrast, maintained vascular tone. Similar *in vitro* observations have been made by others with these preservatives in investigations of the vascular actions of naloxone thus validating our findings.[6,7] As an alternative hypothesis, Lanier *et al.* have shown that succinylcholine causes EEG

arousal with a secondary increase in CBF and intracranial pressure (ICP), but no distinction was made whether or not the succinylcholine was preservative-free.[8] We therefore determined in human volunteers if these preservatives cause an increase in CBF and CBFV. We found no changes in either.

Inhalational ^{133}Xe CBF has been extensively used both by ourselves and others and found to give reproducable CBF values (test-retest variability ± 4%).[5,9] Although there are concerns about extracerebral contamination causing distortion and cross-contamination between hemispheres, noninvasive ^{133}Xe CBF has been reliable when these factors have been taken into account.[5,9] However, one of the disadvantages of the technique is that CBF is averaged over 15 min and the initial slope index (ISI) over 2–3 min. Since Cottrell *et al.* found that in cats the rise in ICP was intense, but short-lived (10–15 sec) following succinylcholine, it is possible that we could have missed a rapid transient rise in CBF with this method.[1]

The objective of the second part of this study was to address the above potential problem. Transcranial Doppler provides a non-invasive instantaneous measure of blood flow velocity in the vessel under view.[10] Although there may be a poor correlation between absolute CBF measurements and MCA velocity, previous work has shown that MCA velocity measurements give an accurate indication of relative change in CBF.[11,12] A change in the peak and mean Doppler MCA flow velocity would have implied vasodilatation. No such change was found in our study. It is possible that if cerebral metabolic rate were decreased and flow and velocity remained unchanged, that the parabens had uncoupled the two by vasodilatation. Although we did not measure cerebral metabolism, no subject experienced any central nervous system signs or symptoms such as drowsiness which would suggest metabolic depression. We also did not monitor end-tidal or arterial carbon dioxide tension. If the subjects hyperventilated concommitant with the paraben administration, this may have prevented or attenuated any vasodilatation. However, none of the subjects was seen to hyperventilate.

There is some evidence that the effect of succinylcholine on ICP in humans may follow a bimodal or trimodal distribution.[1] Our sample size was small enough that all our subjects except for one may have been in the non-reactive subset of this postulated population. However, as this one subject did not demonstrate a similar response on retesting as part of the CBFV group, the increase in ^{133}Xe CBF probably represents a random event. Furthermore, a recent *in vivo* study in cats with and without elevated ICP also could not demonstrate any adverse effects of the paraben preservatives thus supporting our negative findings.[13] However, both our subjects and the cats had normal cerebral vasculature; the influence of the paraben preservatives may be different in the presence of cerebral dysfunction and impaired autoregulation.

Since the *in vitro* vasodilatory effects of the paraben preservatives have been shown in independent laboratories and the absence of *in vivo* effects has also now been shown by independent groups, an attempt at reconciling these findings is necessary.[4,6,7,13] We have excluded pH changes in the waterbath as a cause of vasodilatation. The concentrations of parabens used in our *in vitro* study were based on an estimate of their initial distribution volume and the assumption that no metabolism took place before reaching the brain. Such assumptions were made because we were unable to find relevant data on plasma concentrations in humans. Perhaps one or both of these assumptions are incorrect. The study on which our assumptions of no metabolic degradation in the plasma was based was performed 35 yr ago and used intravenous doses of parabens (50–95 $mg \cdot kg^{-1}$) that far exceed what is currently found in clinical practice.[14] Perhaps these factors led to the erroneous conclusion that the preservatives are only slowly (over six hours) cleared from the plasma by liver esterases and not by plasma esterases. If plasma esterases do indeed play a role in clearance, then a substantial amount of drug metabolism could take place before the bolus reaches the cerebral vasculature. At the very lowest concentrations we studied *in vitro*, vasodilatory effects were not seen.[4]

This study does not exclude the possibility that the paraben preservatives could increase ICP. Transcranial Doppler measures velocity of flow in the MCA, a major cerebral conducting vessel on the surface of the brain. ^{133}Xenon CBF measurements are heavily weighted by the major surface conducting vessels. However, only about 15% of the cerebral blood volume is contained within the cerebral arterial system, the remainder being on the venous side.[15] Thus failure to show any effect on the arterial vessels does not preclude an effect on the venous system which would have a far greater impact on cerebral blood volume and thereby ICP.

In summary, we found that the preservatives methylparaben and propylparaben do not increase CBF and CBFV. We conclude that it is unlikely that the rise in ICP seen with succinylcholine is caused by cerebral arterial vasodilatation from the preservatives methylparaben and propylparaben.

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