PRELIMINARY INVESTIGATION INTO A NEW METHOD OF ASSESSING THE QUALITY OF ANAESTHESIA: THE CARDIOVASCULAR RESPONSE TO A MEASURED NOXIOUS STIMULUS

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SUMMARY

It is suggested that the autonomic response to noxious stimulation may be measured during anaesthesia. The response may be marked despite considerable depression of cortical activity as measured by the cerebral function monitor. Preliminary results suggest that large doses of narcotic analgesics reduce the autonomic response to noxious stimulation and this may be used as a test to compare the potency and duration of action of narcotic drugs during anaesthesia. It is possible that the measurement of beat-to-beat variation in heart rate may be used to monitor autonomic nervous system activity and, indirectly, the degree of stress during surgery, provided that the efferent limb of the reflex arc remains intact. With the aid of the cerebral function monitor and with an index of reflex response to noxious stimulation it should be possible to monitor the effect of anaesthesia on the central nervous system more precisely.

During the search for a suitable total i.v. anaesthetic technique the cerebral function monitor has been used to assess the degree of central depression so that patients were neither aware nor anaesthetized unnecessarily deeply (Dubois et al., 1978). The cerebral function monitor reveals a consistent pattern of change during i.v. anaesthesia and this is particularly so when Althesin or barbiturate agents are used. After induction of anaesthesia, an increase in the rate of administration of these drugs depresses progressively the cerebral function trace and this change may be used to quantify the depth of unconsciousness.

However, depression of cerebral activity does not depress invariably the patient’s reflex response to noxious stimuli, and an increased dose of Althesin may lead to a prolonged recovery without improvement in the quality of anaesthesia. Movement in response to surgical stimulation was reported in 25% of patients anaesthetized with an i.v. technique using Althesin with fentanyl or pethidine (Savege et al., 1975). Movement may be abolished by the use of a myoneural blocking drug. These responses may be reduced or abolished by the use of narcotic supplements (Mushin and Rendell-Baker, 1949; Siker, 1956; Loder, 1957; Davies, 1957; Dundee et al., 1969; Holmes, 1976). However, it has always been difficult to define the clinical indications for giving increments of an analgesic (Siker, 1956; Holmes, 1976).

In this study, preliminary experiences in the use of a test of cardiovascular reflex activity are described.

METHOD

Ethical committee approval was obtained for this study. Healthy, unpremedicated patients were selected and informed consent was obtained. Biparietal needle electrodes were inserted into the scalp for measurement of "cerebral function". About 40 min before elective surgery the patient was anaesthetized with a standard dose of Althesin (50 μg kg⁻¹), the trachea was intubated after the administration of pancuronium 6–8 mg and the lungs were ventilated with oxygen in air with a tidal volume of 7 ml kg⁻¹ and a rate of 14 b.p.m.

Anaesthesia was maintained with a continuous infusion of either 10 or 20% Althesin in saline. The rate of administration was controlled by a pump and
varied according to changes observed with the cerebral function monitor.

After the patient was anaesthetized, a cannula (Abbocath 20 g) was inserted in the dorsalis pedis artery. Arterial pressure was measured continuously by a Gaeltec miniature transducer and displayed on a Devices M19 recorder. Instantaneous pulse rate (heart rate) was measured from the arterial pressure signal and displayed on a continuous recording. At intervals blood was sampled from the arterial cannula for the measurement of $P_{CO_2}$ and the concentration of alphaxalone. A noxious stimulus was applied at various stages of anaesthesia and following the administration of various analgesic adjuvants in order to study the nature and the extent of the response in terms of change in arterial pressure and heart rate. The stimulus used was pressure ($78.5 \text{ N mm}^{-2}$) applied by an algometer over the antero–medial surface of the tibia for 10 s. On one or two occasions pressure was applied to other areas such as the skin over the supraorbital ridge. The reactivity of the peripheral blood vessels was tested in several patients by the administration of methoxamine 1–2 mg i.v. before and after the administration of the analgesic agent.

RESULTS

Figure 1 illustrates the response to noxious stimulation during anaesthesia when cerebral function was being depressed progressively and the blood concentration of Althesin was increasing. The initial part of the trace suggests that the patient was anaesthetized only lightly, with a narrow band of relatively high voltage activity. After increasing the infusion rate the level of cerebral activity was depressed as indicated by broadening (increased variation of activity) and lowering of the trace (decreased voltage). Initially, arterial pressure and heart rate varied continuously, probably as a result of variations in autonomic tone. A noxious stimulus (S) produced an increase in arterial pressure and heart rate. As anaesthesia was deepened and cerebral function was depressed further, arterial pressure and heart rate became less variable. However, another stimulus produced a marked increase in arterial pressure and heart rate. "Reverberating" changes continued for about 5 min as if the autonomic nervous system had been aroused. In the absence of further stimulation and as anaesthesia was deepened, the response faded. However, stimulation several minutes later at an even deeper level of central depression still produced a change in heart rate and arterial pressure.

Figure 2 illustrates measurements in a second patient in whom anaesthesia was deepened progressively by Althesin administered by both bolus injection and continuous infusion. Changes in the cerebral function trace indicate progressive cerebral
depression as the blood concentration of Althesin increased. During light anaesthesia (initial section of the trace) heart rate and arterial pressure were continuously variable. Noxious stimulation of the skin over the supraorbital ridge (Sa) or by movement of the endotracheal tube (Sb) produced an increase in arterial pressure and heart rate. An increment of Althesin and an increased infusion rate depressed cerebral activity and reduced arterial pressure. At the same time both heart rate and arterial pressure became less variable. However, stimulation over the tibia (Sc) or over the supraorbital ridge (Sa) still produced marked changes in heart rate and arterial pressure. The response was diminished but not prevented after further stimulation at a lower level of cerebral activity. Finally, this patient was given a relatively small dose of fentanyl and about 4 min later further stimulation over the supraorbital ridge produced a diminished response.

In figure 3 the cerebral function monitor trace suggests considerable cortical depression which became only slightly more depressed during the course of the study. Initially there were two marked cardiovascular responses to noxious stimulation. Four doses of fentanyl 0.1 mg were administered at approximately 4½-min intervals with a noxious stimulus applied just before the second, third and fourth doses. The changes in heart rate and arterial pressure were reduced progressively. In contrast, the change in arterial pressure following two doses of methoxamine (M), administered one before and one after the fentanyl, were similar.

In a fourth patient a large dose of fentanyl almost prevented the cardiovascular response to noxious stimulation (fig. 4). In contrast, the response to methoxamine was not affected. A feature in this patient which is similar to changes in the third patient is the change in the pattern of arterial pressure and heart rate from one of continuous variation before fentanyl to one of precise regulation afterwards.

Marked or total suppression of the cardiovascular response to this noxious stimulus has been noted in all of five patients who received doses of fentanyl of 0.6 mg or greater. One patient received morphine 2 mg kg⁻¹ with resultant complete suppression of response.

The effects of nitrous oxide may be studied in a similar manner. In figure 5 is shown the effect of administering 67% nitrous oxide to a patient during an infusion of Althesin, namely a reduction in variation in heart rate and arterial pressure, but not prevention of a response to noxious stimulation, although the size
of the response was diminished. During this study the infusion of Althesin remained constant but the blood concentration of Althesin continued to increase slightly and cortical activity as recorded by the cerebral function monitor was depressed further at the time of administration of nitrous oxide.

**DISCUSSION**

Of our two methods of monitoring the central nervous system, one reflects cerebral activity and under certain conditions this may be used to assess the level of unconsciousness. The other detects reflex response to noxious stimulation. It is clear that variations in
cerebral activity do not necessarily correlate with variations in the cardiovascular response to noxious stimuli. Althesin appears to be a potent cerebral depressant, but has much less effect on cardiovascular reflexes. In contrast, fentanyl may obtund the cardiovascular response to noxious stimulation whilst cerebral activity is increasing (fig. 4). This suggests that drugs such as Althesin should be given only to depress consciousness, and that larger doses will not improve the quality of anaesthesia, but merely delay recovery.

The application of a measured noxious stimulus may evoke clear and related changes in arterial pressure and heart rate. Presumably, this is an autonomic reflex response (King et al., 1951; DeVault, Greifenstein and Harris, 1960; Prys-Roberts et al., 1971). As the response appears to be variable, it is not known, at this stage, whether it can be quantified or must be considered an "all or none" phenomenon. Repeated doses of fentanyl seem to depress the response progressively. This suggests that quantification is possible especially if more precise methods of stimulation are developed. It is impossible to provide repeated identical stimuli using tibial pressure. Persistent pressure on one area may cause tissue damage and alter the effect of successive stimuli. Alternatively, changing sites over the area of the tibia will change inevitably the character of the stimulus. Although direct nerve stimulation would probably be more satisfactory, it seems likely that nerve damage may develop without any obvious signs in anaesthetized patients.

The continuous variation in heart rate and arterial pressure seen during light anaesthesia is presumably also the result of autonomic activity. Depression of the latter is likely to be the explanation for the abolition of variation in heart rate and arterial pressure observed as anaesthesia is deepened or after administration of narcotic analgesic drugs. This change may be used for monitoring autonomic activity during surgery.

However, a number of drugs might prevent the cardiovascular responses to noxious stimulation by acting at some point on the efferent limb of the reflex arc. This would be misleading. Beat by beat variation in heart rate and arterial pressure would be abolished whilst afferent nerve traffic would be unaffected and other components of the response to noxious stimulation would continue unabated. So far as we are aware fentanyl has no direct action on peripheral blood vessels. However, when large doses are administered, arterial pressure frequently decreases and the cause for this may be vasodilatation. The finding that cardiovascular changes in response to noxious stimulation were reduced also following fentanyl increased the suspicion that fentanyl may block the vascular response at the periphery. However, the increase in arterial pressure in response to methoxamine indicates that a-adrenergic receptors are not blocked (Harrison et al., 1964). In addition, the decrease in heart rate that accompanies the increase in pressure indicates that the baroreceptor reflex is intact and, presumably, that autonomic ganglia are not blocked either. It might be argued that autonomic reflex responses during anaesthesia are a useful indication that the patient retains certain "protective" mechanisms. However, several studies have suggested that patients pursue a better clinical course in the period after operation if reflex responses to surgery are reduced by the administration of analgesic drugs (Mushin and Rendell-Baker, 1949; Loder, 1957; Dundee et al., 1969; Henderson and Parbrook, 1976). Hypertension and tachycardia in response to noxious stimulation during anaesthesia have been reported (King et al., 1951; Wycuff, 1960; DeVault, Greifenstein and Harris, 1960; Takeshima, Noda and Higaki, 1964; Forbes and Dally, 1970; Prys-Roberts et al., 1971; Vaughan, Cobb and Roa, 1974). Such cardiovascular changes increase cardiac work and oxygen consumption (Sonnenblick and Skelton, 1971). These effects may be harmful especially in hypertensive patients. Arrhythmia in response to stimuli occur also and may initiate serious consequences (Colon-Yordan, Mackrell and Stone, 1953; DeVault, Greifenstein and Harris, 1960; Prys-Roberts et al., 1971).

Furthermore, cardiovascular changes are not the sole effect of the autonomic response to noxious stimulation. In addition, there may be a wide range of metabolic changes (Hume and Egdaahl, 1959), loosely termed "the stress response", which are affected principally by the autonomic nervous system with the adrenal cortex playing a purely permissive role (Johnston, 1973; Wilmore, 1976). The stress response has always been considered an important biological defence mechanism (Johnston, 1973). This view, however, is being questioned increasingly as more potentially harmful consequences of stress are proposed, some of which are listed in table I. In addition, Kehlet and Binder (1973) have shown that reduced secretion of cortisol during surgery does not result necessarily in clinical complications. Other workers have prevented the metabolic responses of stress during surgery by various techniques including the use of local analgesia (Gordon, Scott and Robb, 1973),
large doses of morphine (George et al., 1974) and fentanyl (Arroyo and Nalder, 1976) without any apparently harmful consequences. Whatever the value of the stress response it is clearly an important reaction that has always been difficult to monitor. The usual methods, of measuring changes in the blood concentration of cortisol or catecholamines, provide only retrospective information.

We propose that the cardiovascular response to noxious stimulation is evidence that the reflex arc is "open" and that the metabolic effects of stress will be induced if noxious stimulation continues. The variation in heart rate that occurs from beat to beat indicates the level of autonomic activity and may well correlate with the extent of the metabolic response to stress. If this is so, stress could be monitored continuously by a simple non-invasive technique.

This preliminary work has shown that narcotic analgesia can attenuate the autonomic response to noxious stimulation. This method might be used to evaluate the potency and duration of effect of different analgesic agents during anaesthesia. However, the "patency" of the efferent limb of the reflex must be tested for each different type of anaesthetic sequence before the absence of a response to noxious stimulation can have any significance.

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Recherche préliminaire sur une nouvelle méthode d'évaluation de la qualité de l'anaesthésie: Reaction cardiovasculaire à un excitant nocif

RESUME

On pense que la réaction autonome à un excitant nocif peut être mesurée pendant l'analgesie. La réaction peut être prononcée en dépit de la dépression considérable de l'activité corticale telle qu'on peut la mesurer par l'appareil de surveillance de la fonction cérébrale. Les résultats préliminaires laissent penser que de fortes doses d'analgésiques narcotiques diminuent la réaction autonome à un excitant nocif et on peut l'utiliser comme moyen d'essai pour comparer l'efficacité et la durée d'action des médicaments narcotiques pendant l'anaesthésie. Il est possible que la mesure des variations dans les battements de cœur soit utilisée pour surveiller l'activité du système nerveux autonome et, indirectement, le degré du stress pendant l'intervention chirurgicale, à la condition que le membre efférent de l'arc réflexe demeure intact. Grâce à l'appareil de surveillance de la fonction cérébrale et avec un index de la réaction du réflexe à un excitant nocif il devrait être possible de surveiller plus étroitement l'effet de l'anaesthésie sur le système nerveux central.

Vorläufige Untersuchung einer neuen Methode zur Qualitätsbeurteilung von Narkosen: Die kardiovaskuläre Reaktion auf einen abgemessenen schädlichen Stimulus

ZUSAMMENFASSUNG

INVESTIGACION PRELIMINAR DE UN NUEVO METODO PARA LA EVALUACION DE LA CALIDAD DE LA ANESTESIA: LA RESPUESTA CARDIOVASCULAR A UN ESTIMULO NOCIVO MEDIDO

SUMARIO
Se sugiere que la respuesta autónoma a un estímulo nocivo puede medirse durante la anestesia. La respuesta puede ser marcada a pesar de una apreciable depresión de la actividad cortical según las mediciones del monitor de la función cerebral. Los resultados preliminares sugieren que en grandes dosis los analgésicos narcóticos reducen la respuesta autónoma al estímulo nocivo y esto puede emplearse como una prueba para la comparación de la potencia y la duración de la acción de las drogas narcóticas durante anestesia. Es posible que midiendo las variaciones en la rapidez de los latidos del corazón, pueda observarse la actividad del sistema nervioso e indirectamente, el grado de “stress” durante la cirugía, siempre que el miembro eferente del arco reflejo permanezca intacto. Con la ayuda del monitor del funcionamiento cerebral y con un índice de respuesta refleja ante un estímulo nocivo, debería ser posible observar el efecto que ejerce la anestesia sobre el sistema nervioso central en forma más precisa.