KETAMINE AND PLASMA CATECHOLAMINES

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SUMMARY

Changes in blood pressure, pulse rate and plasma catecholamine levels during induction of anaesthesia with ketamine 2 mg/kg were studied in 13 adults and 12 children. Six adults and 6 children received only ketamine, whereas in 7 adults and 6 children ketamine was followed by suxamethonium 1 mg/kg, intubation and nitrous oxide/oxygen mixture. Both kinds of induction caused a rise in the systolic blood pressure, which amounted to 40–50 mm Hg in adults and to about 20 mm Hg in children. The only significant increase in total plasma catecholamine levels (about 50 per cent above resting level) occurred 2 minutes after ketamine-suxamethonium induction in adults. The increase was due to both noradrenaline and adrenaline. The results suggest that the ketamine-induced pressure response in man may be partly due to sympathetic stimulation.

Ketamine has a biphasic action on the cardiovascular system; an initial depression is followed by stimulation (Dowdy and Kaya, 1968). The initial depression, seen especially after higher doses of the drug, is attributable to a direct negative inotropic effect on the myocardium (Dowdy and Kaya, 1968). The stimulant action, which appears as an increase in arterial pressure and heart rate (Traber, Wilson and Priano, 1968), is more prominent after clinical anaesthetic doses (Faithfull and Haider, 1971). In dogs the positive chronotropic response and part of the pressor response seem to be related to blockade of the vagus nerve (Traber, Wilson and Priano, 1970a).

But central sympathetic stimulation may also be responsible for the pressor response since this is abolished by high epidural block (Traber and Wilson, 1969) or by pretreatment with the ganglion blocking agent, hexamethonium (Traber, Wilson and Priano, 1970b). It has been suggested that the central sympathetic stimulation is due to a diminution in the frequency of discharge of baroreceptors (Dowdy and Kaya, 1968). In accordance with these observations Dundee and associates (1971) reported an increase in plasma catecholamine levels after ketamine injection in 14 of 17 patients. More detailed information about the behaviour of catecholamines after ketamine injection does not, however, appear to have been reported. We have therefore measured plasma catecholamine levels after ketamine administration in adults and children.

PATIENTS AND METHODS

There were 13 adults scheduled for elective general surgery and 12 children scheduled for elective ophthalmic surgery. Table I shows their distribution between the two treatment groups. The general condition of the patients was good, and their cardiovascular function was normal, as shown by clinical and X-ray examinations in all patients and by e.c.g. (12 leads) in adult patients. All were given preanaesthetic medication of atropine 0.01 mg/kg and pethidine 1 mg/kg, by intramuscular injection, 30–45 min before induction. All measurements were performed in the induction room. The largest accessible vein was cannulated and a slow infusion of 10 per cent invert sucrose started. When cardiovascular stability had been achieved (three consecutive similar readings of arterial pressure and heart rate) control blood samples were drawn. Anaesthesia was then induced with ketamine 2 mg/kg injected into the side arm of the drip over 90 sec. In one group in each age class (table I), no other agents were used during the 7 min recording period. In the other two groups suxamethonium 1 mg/kg was given immediately after induction and anaesthesia was maintained after endotracheal intubation with a nitrous oxide/oxygen mixture (5 and 2 l./min) using a semi-closed system, ventilation being controlled manually. Anaesthesia was continued in the usual manner, after the recording period.

Arterial pressure and pulse rate were measured before and 2, 5 and 7 min after induction. The former was measured to the nearest 5 mm Hg by auscultation, using the same arm. The same observer...
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TABLE I. Sex, age, weight, height of patients and the mean values with SE for preanaesthetic plasma catecholamine levels in the different groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Sex M/F</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Plasma catecholamines (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA+A</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine 2 mg/kg</td>
<td>6</td>
<td>3/3</td>
<td>47 ± 6.4</td>
<td>71 ± 9.1</td>
<td>166 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>Ketamine 2 mg/kg +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>suxamethonium 1 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.73 ± 0.08</td>
</tr>
<tr>
<td>Children</td>
<td>7</td>
<td>4/3</td>
<td>44 ± 13.0</td>
<td>66 ± 9.3</td>
<td>171 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Ketamine 2 mg/kg</td>
<td>6</td>
<td>3/3</td>
<td>12 ± 1.0</td>
<td>41 ± 4.3</td>
<td>152 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>Ketamine 2 mg/kg +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58 ± 0.10</td>
</tr>
<tr>
<td>suxamethonium 1 mg/kg</td>
<td></td>
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<td></td>
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<td>0.58 ± 0.10</td>
</tr>
</tbody>
</table>

made the measurements, taking care that the site of auscultation was always the same. Lead II of the electrocardiogram was monitored continuously in adult patients.

Catecholamine determinations.

Blood samples for catecholamine measurements were collected from the cannulated cubital vein before and at 2 and 5 min after induction.

The details of the technique used for sampling and quantitative determination of adrenaline (A) and noradrenaline (NA) in the plasma were the same as described previously (Tammisto et al., 1971). The method was based on the principles described by Vendsalu (1960).

For each determination an 18 ml sample of blood was needed. Perchloric acid was used in the deproteinization of the plasma. For purification of the extracts Dowex 50 × 4 columns were used in hydrogen form. The elution was performed with N-hydrochloric acid. The A and NA in the eluate were determined spectrophotofluorometrically after oxidation with potassium ferricyanide and subsequent rearrangement to adrenolutine and noradrenolutine. The fluorescences of the lutines of A and NA were measured at different wavelengths. A standard Aminco-Bowman spectrophotofluorometer was employed. Faded blanks and reagent blanks were calculated as described by Vendsalu (1960). Internal standards were generally used by adding a known amount (0.005–0.2 µg) of A or NA or both to the plasma samples. Recovery by the method was 82 ± 4 (SE) % of A and 78 ± 6 (SE) % of NA. Duplicate extractions on plasma samples gave results that varied no more than 10%.

RESULTS

The mean changes in arterial pressure, heart rate and total plasma catecholamines in adults and child-

FIG. 1. The change in arterial systolic and diastolic blood pressure, heart rate and total plasma catecholamine levels in the four different groups. Mean ± SE.
difference between the groups was statistically significant (P<0.001). After ketamine and suxamethonium the mean maximum increases were 39±11 mm Hg and 18±5 mm Hg respectively but here the difference between the groups was not statistically significant (P>0.05). The diastolic blood pressure behaved similarly to the systolic pressure but the changes were slightly less. The increase in heart rate was similar in adults and in children.

Ketamine 2 mg/kg
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Ketamine 2 mg/kg + Suxamethonium 1 mg/kg

FIG. 2. The change in plasma noradrenaline and adrenaline in the four different groups. Mean ± SE.

The level of total plasma catecholamines increased statistically significantly after ketamine with suxamethonium induction in adults, but not in children. The increase amounted to about 50% (0.37±0.12 (SE) µg/l.; P<0.05) 2 min after induction. Both noradrenaline and adrenaline levels were raised (fig. 2), but the increase in adrenaline level alone (0.22±0.07 µg/l.) was statistically significant (P<0.05). After ketamine alone, the increase of total catecholamines was not statistically significant in adults. An insignificant increase in noradrenaline levels was also measured in children 5 min after ketamine+ suxamethonium. In children the difference in the preanaesthetic adrenaline levels between the two groups (table I) was statistically significant (P<0.05). This surprising difference is reflected also in total plasma catecholamines, though here the difference between the groups was not statistically significant.

DISCUSSION

The hypertensive action of ketamine has been considered to be alarming, especially in old patients, in whom the tolerance of the cardiovascular system cannot be guaranteed (Corssen and Domino, 1966). In the present study the increase in arterial pressure was more pronounced in normotensive adults than in children, but we did not encounter difficulty in consequence of this cardiovascular stimulation. This is in accordance with the results reported by Zohairy and Siddiqui (1971), Knox and associates (1970) and Gjessing (1968). Arrhythmias were not observed in the present series, but the electrocardiogram was monitored continuously only in the adults. This finding is supported by the results of Faithfull and Haider (1971), who employed ketamine for cardiac catheterization procedures in patients with cardiac abnormalities and did not observe any irregularities of rhythm. It has also been proposed that the drug has anti-arrhythmic properties (Dowdy and Kaya, 1968). Although only the pressor effect of ketamine has been observed in most of the series published, yet there are some data on cardiovascular depression. Dowdy and Kaya (1968) found cardiovascular depression in dogs followed after 1-3 min by the pressor effect in "fewer cases" as an initial reaction to ketamine. Gjessing (1968) also reported a fall in systolic blood pressure after ketamine 1 mg/kg in one patient of forty. Faithfull and Haider (1971) observed hypotension in 17.5% of children with different degrees of cardiac abnormalities, which in 15% they considered as attributable to ketamine. In the present study we found in one patient a decrease of 55 mm Hg in systolic pressure followed in 5 min by a pressor response up to 25 mm Hg above the initial level.

The cause of the ketamine-induced hypertension has been assumed to depend partly on the central sympathetic stimulation (Traber and Wilson, 1969) possibly caused by a diminution of frequency discharge of baroreceptors (Dowdy and Kaya, 1968). In the present study the increase in plasma catecholamines was equivocal after ketamine alone but statistically significant after ketamine+ suxamethonium in adults.

In the latter group the short-lasting increase in catecholamine levels might also be related to laryngoscopy and intubation, since these procedures have been shown to cause sympathetic stimulation


KETAMINE ET CATECHOLAMINES PLASMATIQUES

**SUMMARY**

Les variations de la pression artérielle, de la fréquence cardiaque et du taux des catécholamines plasmatiques, observées au cours de la phase d'induction d'une anesthésie par la Ketamine (2 mg/kg) ont été étudiées chez treize adultes et douze enfants. Six adultes et six enfants ont reçu uniquement la Ketamine, tandis que l'administration de celle-ci a été suivie de celle de suxaméthonium (1 mg/kg), d'une intubation et de l'inhalation du mélange protoxyde d'azote et oxygène chez sept adultes et six enfants. Les deux types d'induction anesthésique ont entraîné un accroissement de la pression sanguine qui a été de 40 à 50 mm Hg chez les adultes et de 20 mm Hg environ chez les enfants. La seule amplification significative des taux des catécholamines plasmatiques totales (de 50 pour
cent environ au-dessus du taux noté au repos) s’est produite deux minutes après l’induction anesthésique par la Kétamine et le suxaméthonium, chez les adultes. Cette augmentation était due à la fois à la noradrénaline et à l’adrénaline. Les résultats obtenus suggèrent que la réponse tensionnelle induite par la Kétamine chez l’Homme, peut provenir, pour une part, d’une stimulation sympathique.

KETAMIN UND PLASMAKATECHOLAMINE

ZUSAMMENFASSUNG
An 13 Erwachsenen und 12 Kindern wurden während der Einleitung einer Ketaminarkose (2 mg/kg) Veränderungen des Blutdrucks, der Herzfrequenz und der Plasmakatecholaminspiegel untersucht. Sechs Erwachsene und sechs Kinder erhielten Ketamin allein, während bei sieben Erwachsenen und sechs Kindern auf das Ketamin noch Suxamethonium (1 mg/kg), Intubation und ein Gemisch von Lachgas/Sauerstoff folgte. Beide Arten der Einleitung verursachten einen Anstieg des systolischen Blutdrucks, der bei den Erwachsenen 40–50 mm Hg und bei den Kindern etwa 20 mm Hg betrug. Der einzig signifikante Anstieg der Plasmakatecholamin-Gesamtspiegel (etwa 50% über dem Ruhespiegel) stellte sich 2 Minuten nach der Einleitung mit Ketamin/Suxamethonium bei Erwachsenen ein. Der Anstieg war sowohl auf Noradrenalin als auch auf Adrenalin zurückzuführen. Die Ergebnisse lassen darauf schließen, daß die durch Keta
min erzeugte Blutdruckreaktion beim Menschen zum Teil auf Sympathikuseregression zurückzuführen sein mag.

CETAMINA Y CATECOLAMINAS DEL PLASMA

RESUMEN
Fueron estudiados en trece adultos y doce niños los cambios en la presión arterial, frecuencia del pulso y niveles de las catecolaminas del plasma durante la inducción de anestesia con cetamina (2 mg/kg). Seis adultos y seis niños recibieron solamente cetamina, en tanto que en siete adultos y seis niños la cetamina fue seguida por suxamet
tonio (1 mg/kg), intubación y una mezcla de óxido intraso/oxígeno. Ambas clases de inducción causaron una elevación en la presión arterial sistólica, que fue de 40–50 mm Hg en los adultos y aproximadamente 20 mm Hg en los niños. El único incremento significativo en los niveles de catecolaminas plasmáticas totales (aproximada
mente el 50 por ciento por encima del nivel de reposo) ocurrió 2 minutos después de la inducción con cetamina-
suxametonio en adultos. Este incremento era debido a noradrenalina y adrenalina. Estos resultados sugieren que la respuesta de la presión arterial inducida por cetamina pudiera ser parcialmente debida a una estimulación sim
pática.