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EFFECT OF DOSE AND PREMEDICATION ON INDUCTION COMPLICATIONS WITH ETOMIDATE

A. HOLDCROFT, M. MORGAN, J. G. WHITWAM AND J. LUMLEY

"—and when she was good she was very very good
but when she was bad she was horrid."
LONGFELLOW

SUMMARY

The induction characteristics of etomidate, a new i.v. hypnotic agent, were studied in 400 patients. Two hundred were premedicated with atropine and anaesthesia was induced with 0.2, 0.25, 0.3 or 0.35 mg/kg of etomidate. The remainder received one of four standard premedications and anaesthesia was induced with etomidate 0.3 mg/kg. Involuntary muscle movements occurred in more than 60% of patients receiving atropine alone. The frequency was reduced in the second group, but remained unacceptable in over 8% of patients. The incidence of other excitatory phenomena, such as cough and hiccup, was 10% approximately. Cardiovascular changes were minimal and no serious allergic phenomena were observed. Nausea and vomiting occurred after surgery in up to 30% of patients and was unrelated to the dose of etomidate or to premedication. Pain on injection occurred in up to 80% of patients when the drug was injected into small peripheral veins and occurred in more than 7% when using more proximal veins.

Etomidate (R-(+)-ethyl-1-(pentylethyl) 1H-imidazole-5-carboxylate sulphate (fig. 1)) is a recently introduced i.v. induction agent. The drug is water-soluble and is presented as a 0.15% solution of pH 3 units. Animal work by Janssen and colleagues (1971) suggested that etomidate caused rapid induction of anaesthesia and had a wider margin of safety than thiopentone, methohexitone and propanidid.

Preliminary work in man by Doenicke, Kugler and others (1973) and Doenicke, Wagner and Beetz (1973) suggested that, at a dose of 0.3 mg/kg, etomidate would induce hypnosis with minimal cardiorespiratory effects. They observed that the drug caused involuntary movements, which may be severe, but their incidence could be reduced by diazepam. Morgan, Lumley and Whitwam (1975) confirmed that the optimum dose of etomidate was approximately 0.3 mg/kg, and observed a high incidence of involuntary muscle movement.

The purpose of the present study was to investigate the effect of the dose of etomidate and premedication on its induction characteristics.

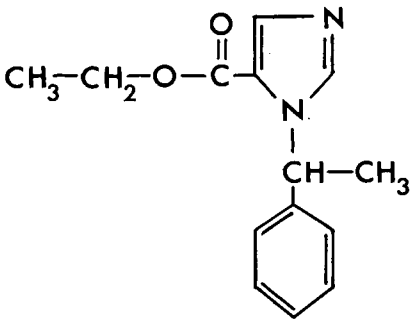

FIG. 1. Etomidate.

METHODS

Etomidate was used as a single i.v. induction agent for non-emergency surgery, excluding cardiothoracic surgery and surgery in pregnancy. The following observations were made: (1) Involuntary muscle movements, which were classified as (a) severe, resembling a generalized convulsion, (b) moderate, when there was contraction of a large group of muscles or less severe generalized muscle activity, and (c) mild, when restricted to slight twitching involving one or more limbs which did not interfere with induction. (2) Respiratory disturbances such as cough, hiccup and laryngospasm. (3) Pulse rate and arterial pressure (by palpatation) at 1-min intervals for 5 min. (4) Any evidence of an allergic reaction. (5) Because of the

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increase in muscle tone associated with etomidate, serum potassium concentrations were measured in 40 consecutive patients who were premedicated with atropine only. A control sample of venous blood was taken, and further samples were taken at 1, 3, 5 and 10 min after the administration of etomidate. The 1-min sample was taken before any other agents were given. In 20 of these patients, suxamethonium 1 mg/kg was given immediately following the 1-min sample. Serum potassium estimations were made, using serum from clotted blood, with an EEL 150 Clinical Flame Photometer (Evans, Electroselenium, Halstead, Essex).

Varying dose. Two hundred patients received atropine 0.6 mg i.m. 1 hr before operation. They were allocated randomly to receive 0.2, 0.25, 0.3 and 0.35 mg/kg of etomidate, which was injected i.v. during a period of 30 sec.

Premedication. A further 200 patients were allocated randomly to receive one of the following drug combinations 1 hr before operation: (1) Papaveretum 10–20 mg and hyoscine 0.2–0.4 mg; (2) pethidine 50–100 mg and atropine 0.6 mg; (3) pethidine 50–100 mg, promethazine 12.5–25 mg and atropine 0.6 mg; (4) diazepam 10–20 mg orally and atropine 0.6 mg i.m. The doses were varied according to the individual's requirements and all these patients received, for induction of anaesthesia, etomidate 0.3 mg/kg.

After induction, in both groups, anaesthesia was maintained with nitrous oxide in oxygen, other agents being administered according to the type of operation. Each patient was visited on the day following the operation to ascertain the occurrence of nausea and vomiting, and thrombophlebitis at the site of injection.

RESULTS

The age, weight and physical status of the 400 patients in the study are shown in table I.

Involuntary movement. The influence of the dose of etomidate on the occurrence of involuntary muscle movements is shown in table II. Although moderate and severe movements were most frequent (40%) with the highest dose of etomidate there was no significant correlation between these movements and the dose of the drug ($P > 0.05$). The frequency of involuntary

TABLE I. *Age and weight (± SD) of patients in each group, and number in each physical status group (ASA classification). Patients who received varying doses of etomidate all premedicated with 0.6 mg atropine. Patients receiving different premedicants all anaesthetized with etomidate 0.3 mg/kg. Fifty patients in each group*

	Dose of etomidate (mg/kg)				Premedication			
Patient data	0.2	0.25	0.3	0.35	Papaveretum + hyoscine	Pethidine + atropine	Pethidine promethazine + atropine	Diazepam + atropine
Age (yr)	51.7 ± 18.4	44.3 ± 18.5	43.0 ± 15.6	46.0 ± 17.2	39.6 ± 17.4	48.5 ± 19.6	45.2 ± 15.0	41.1 ± 17.3
Weight (kg)	62.7 ± 14.7	62.1 ± 11.9	64.0 ± 12.4	63.4 ± 10.8	59.4 ± 14.7	66.5 ± 14.0	61.9 ± 11.3	61.7 ± 12.7
Physical status								
1	35	38	43	39	36	40	36	44
2	7	11	3	6	9	8	9	3
3	6	1	3	4	2	2	4	3
4	2	0	1	1	3	0	1	0

TABLE II. *Frequency (%) of involuntary movement and increased muscle tone related to dose of etomidate and premedication. Those receiving the different premedicants were anaesthetized with etomidate 0.3 mg/kg. Fifty patients in each group*

	Dose of etomidate (mg/kg)				Premedication			
Involuntary muscle movement	0.2	0.25	0.3	0.35	Papaveretum + hyoscine	Pethidine + atropine	Pethidine promethazine + atropine	Diazepam + atropine
None	38	34	36	36	78	62	58	50
Mild	36	34	38	24	14	30	34	32
Moderate	20	26	18	34	6	8	8	14
Severe	6	6	8	6	2	0	0	4
Increased muscle tone	6	2	8	8	2	4	8	12

movements was reduced significantly ($P<0.05$) by the various premedicant drugs (table II), but the least effective in this respect was diazepam and atropine, since movements still occurred in 18% of patients. Of the patients premedicated with atropine alone, 6% developed a generalized increase in muscle tone which was not associated with movement. The lowest frequency of muscle movements (no movements: table II) occurred in patients premedicated with papaveretum and hyoscine, but this was not significantly different ($P>0.1$) from the frequency in patients receiving other types of premedication except atropine 0.3 mg/kg ($P<0.05$).

Respiratory upsets (table III). Hiccup occurred in a small number of patients but was not troublesome. The duration of clinically observed apnoea was prolonged following etomidate 0.35 mg/kg and in those patients who were given papaveretum and hyoscine. The frequency of apnoea was not affected markedly by premedication. Hyperventilation and coughing during induction were not common. Laryngospasm occurred in two patients; it was mild in both and disappeared rapidly.

Cardiovascular effects. The changes in pulse rate and arterial pressure at 1 min after the administration of etomidate, following which other drugs were administered, are shown in table IV. Severe hypotension did not occur and the observed reductions in arterial pressure never required treatment. The most obvious cardiovascular effect was a greater increase in pulse rate in the patients who received atropine alone ($P<0.01$).

Sensitivity reactions. One patient developed an erythematous rash but showed no evidence of serious allergic phenomena such as hypotension or bronchoconstriction. In another three patients a similar rash was observed following either suxamethonium or tubocurarine.

Pain on injection. Eighty-one per cent of patients complained of pain on injection when this was made into small peripheral veins, such as the dorsum of the hand. When injection was made into larger veins on the forearm or at the elbow, the frequency of pain was 44% and 8%, respectively.

Serum potassium (table V). The individual variation in duplicate analyses was no greater than 0.1 m-mol/

TABLE III. *Frequency (%) of respiratory complications related to dose of etomidate and premedication. Patients receiving different induction doses of etomidate were premedicated with atropine alone. Those patients receiving the different premedications were anaesthetized with etomidate 0.3 mg/kg. Fifty patients in each group*

	Dose of etomidate (mg/kg)				Premedication			
Respiratory upset	0.2	0.25	0.3	0.35	Papaveretum + hyoscine	Pethidine + atropine	Pethidine promethazine + atropine	Diazepam + atropine
Hiccup	6	4	2	2	0	2	2	4
Hyperventilation	4	2	2	4	0	2	2	0
Coughing	2	8	2	0	2	2	0	2
Laryngospasm	0	0	0	0	0	0	2	2
Apnoea	4	12	20	12	8	8	2	12
Mean duration (sec)	13	27	23	47	41	20	15	20

TABLE IV. *Frequency (%) of patients showing indicated changes in pulse rate and arterial pressure related to dose of etomidate and premedication. Those receiving the different premedicants were anaesthetized with etomidate 0.3 mg/kg. Fifty patients in each group*

	Dose of etomidate (mg/kg)				Premedication			
Cardiovascular changes	0.2	0.25	0.3	0.35	Papaveretum + hyoscine	Pethidine + atropine	Pethidine promethazine + atropine	Diazepam + atropine
Arterial pressure								
Increase >20 mm Hg	8	6	6	8	4	4	2	6
Decrease >20 mm Hg	8	2	6	10	8	8	8	4
Pulse rate								
Increase >20 beats/min	6	4	14	6	2	0	0	0
Decrease >20 beats/min	0	2	0	0	6	4	4	0

TABLE V. *Changes in serum potassium. Twenty patients in each group. (None of these changes was statistically significant; $P > 0.05$ in each group)*

Patient groups	No.	Control (mean ± SD) (m-mole/litre)	Mean change from control ± SD (m-mol/litre)			
			1 min	3 min	5 min	10 min
No suxamethonium	20	3.80	0.03	−0.01	−0.02	0.002
(1) All patients		±0.33	±0.22	±0.20	±0.23	±0.17
(2) None/mild movements	11	3.90	−0.05	−0.12	−0.06	−0.03
		±0.24	±0.22	±0.15	±0.21	±0.19
(3) Moderate/severe movements	9	3.67	0.13	0.11	0.12	0.03
		±0.39	±0.19	±0.18	±0.23	±0.15
Suxamethonium after 1 min						
(1) All patients	20	4.02	−0.09	0.02	−0.23	−0.045
		±0.34	±0.14	±0.28	±0.24	±0.27
(2) None/mild movements	12	4.15	−0.19	−0.12	−0.04	−0.07
		±0.25	±0.11	±0.21	±0.22	±0.21
(3) Moderate/severe movements	8	3.82	0.03	0.23	0.01	−0.003
		±0.37	±0.08	±0.25	±0.28	±0.35

TABLE VI. *Frequency (%) of postoperative sequelae. Fifty patients in each group*

Postoperative sequelae	Dose of etomidate (mg/kg)				Premedication			
	0.2	0.25	0.3	0.35	Papaveretum + hyoscine	Pethidine + atropine	Pethidine promethazine + atropine	Diazepam + atropine
Nausea alone	4	14	6	12	16	14	8	10
Nausea and vomiting	28	24	30	30	28	30	20	16
Thrombophlebitis	0	2	0	0	0	0	0	0

litre. When etomidate was used alone, the serum potassium concentration at 3 min in those patients who exhibited no or mild muscle movement decreased by about 5% from the control value, whereas in those patients in whom more severe movements occurred, there was an increase of 3%. The changes in serum potassium are shown in table V; none is statistically significant. Even when suxamethonium was administered, moderate or severe muscle movement was observed following induction with etomidate. The mean serum potassium concentration increased by a maximum of 6% (0.23 m-mol/litre), and this was not significant ($P > 0.05$).

Postoperative sequelae (table VI). The dose of etomidate and the premedication had little effect on the occurrence of nausea and vomiting, the latter being slightly more common in those who had received atropine only (28% compared with 24%) and least in those premedicated with diazepam (16%), but this was not statistically significant ($P > 0.1$). Mild thrombophlebitis, which cleared rapidly, occurred after operation in one patient.

DISCUSSION

In patients premedicated with atropine alone, a single induction dose of etomidate was associated with a high frequency of involuntary muscle movement (table II), which subsided rapidly. The combination of intermittent etomidate with nitrous oxide alone to maintain anaesthesia was associated with a persistent increase in muscle tone and involuntary movements and was impractical.

At the highest dose of etomidate (0.35 mg/kg), the frequency of severe and moderate movements was not significantly higher than at the other doses. The most satisfactory dose would appear to be in the region of 0.3 mg/kg, as suggested by Doenicke and others (Doenicke, Kugler et al., 1973; Doenicke, Wagner and Beetz, 1973), since this provides an adequate duration of hypnosis (Morgan, Lumley and Whitwam, 1975),

while a larger dose leads to an increase in the proportion of unacceptable inductions.

In many patients the appearance of excitatory phenomena appeared to be evoked reflexly by stimulation such as results from insertion of an i.v. cannula and the measurement of arterial pressure. The occurrence of muscle movement was reduced markedly by the inclusion of premedicant drugs other than atropine alone ($P<0.01$). Diazepam has been reported to reduce the incidence of these phenomena (Doenicke et al., 1973) and this was confirmed in the present study. The inclusion of opiates in the premedication was associated with an acceptable induction (either no or mild muscle movements) in more than 90% of patients. A reduction of involuntary movements on induction of anaesthesia following opiate premedication has been observed previously with methohexitone, propanidid and Althesin (Dundee and Wyant, 1974).

The administration of suxamethonium is associated with an increase in plasma potassium of the order of 5–6% (Stovner, Endresen and Bjelke, 1972), which may increase to a greater extent in patients suffering from burns or who are in renal failure. Intravenous induction agents, such as methohexitone, tend to reduce the concentration of potassium in the plasma (Bali and Dundee, 1974), and this was the case also, in the present study, in patients who did not exhibit marked muscle movement after the administration of etomidate. However, the appearance of moderate and severe muscle movements reversed this trend and in this group of patients etomidate appears to behave in a manner different from other agents. Where moderate and severe muscle movements occurred following etomidate, in association with the administration of suxamethonium, there was an increase in the plasma potassium concentration of 6% which was similar to that reported by Stovner and colleagues (1972), but in the present study the groups of patients were relatively small and the observed changes were not statistically significant.

Pain during injection was very common when small peripheral veins were used and the drug should be administered to large veins on the forearm. Rowlands (1969) found that the addition of lignocaine to methohexitone solutions reduced the incidence of pain and discomfort from 10% to 1%, and it may be that a similar technique would be successful with etomidate.

The incidence of cough, hiccup and laryngospasm was small and was not dose-related. The incidence and duration of clinically observed apnoea were related to the dose of etomidate, but the incidence was less frequent than has been reported following the administration of thiopentone, methohexitone and Althesin (Whitwam, 1962; Hall, Whitwam and Morgan, 1973).

Etomidate appears to cause minimal cardiovascular effects. In the majority of patients there were only small changes in pulse rate and arterial pressure, and severe hypotension did not occur. Previously, Morgan, Lumley and Whitwam (1975) noted a slight but significant decrease in systolic arterial pressure from the control values during a 5-min period, with no change in pulse rate.

Anaphylactic reactions are being reported more commonly in association with the use of i.v. induction agents. Although four patients in this series developed a rash following etomidate, the cause was uncertain, and there was no associated hypotension or bronchospasm. Doenicke, Lorenz and others (1973) have demonstrated that etomidate, unlike the other i.v. induction agents, does not cause histamine release and this could be a significant advantage of the drug.

In this study, the occurrence of nausea and vomiting appeared to be unrelated to the dose of etomidate or to the premedication, and was only slightly greater than that reported for thiopentone, methohexitone and propanidid (Clarke et al., 1971). Only one of the 400 patients developed thrombophlebitis, which is less than the frequency occurring with the other drugs mentioned above (Carson et al., 1972).

This study was not concerned primarily with recovery following etomidate. However, unlike the barbiturates whose short duration of action is a result of redistribution (Price et al., 1960), etomidate appears to be hydrolysed, which could explain its short duration of action, and in this respect it is similar to propanidid. In the present study, following short procedures, recovery from anaesthesia was rapid and there was no "hangover".

The two major disadvantages of etomidate are pain on injection and muscle movement. When compared with methohexitone (Dundee et al., 1961), the incidence of these muscle movements following the administration of etomidate is influenced less by the dose of the drug and more by premedication.

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EFFET DU DOSAGE ET DE LA MEDICATION PRE-OPERATOIRE SUR LES COMPLICATIONS D'INDUCTION AVEC L'ETOMIDATE

RESUME

Les caractéristiques d'induction de l'étomidate, nouvel agent hypnotique intraveineux, ont été étudiées sur 400 patients. On a administré à 200 d'entre eux de l'atropine comme médication pré-opératoire et l'anesthésie a été obtenue par 0,2, 0,25, 0,3 ou 0,35 mg/kg d'étomidate. Les autres se sont vus administrer l'une de quatre médications pré-opératoires et l'anesthésie a été obtenue par 0,3 mg/kg d'étomidate. Des mouvements musculaires involontaires se sont produits sur plus de 60% des patients ayant reçu uniquement de l'atropine. La fréquence a été moindre chez les patients du second groupe, mais elle est demeurée inacceptable pour plus de 8% des patients. L'incidence des autres phénomènes excitatoires, tels que toux et hoquet a été de l'ordre de 10%. Les variations cardiovasculaires ont été minimales et on n'a observé aucun phénomène sérieux d'allergie. Des nausées et des vomissements se sont produits après l'intervention chirurgicale sur environ 30% des opérés, mais ils n'avaient aucune relation avec la dose d'étomidate ou la médication pré-opératoire. Des douleurs se sont produites au moment de l'injection sur près de 80% des patients, lorsque la médication a été injectée dans les petites veines périphériques et dans plus de 7% des cas lorsqu'on a utilisé des veines plus proximales.

DIE BEZIEHUNG DER BASISNARKOSE-DOSIERUNG ZU DEN EINLEITUNGSKOMPLIKATIONEN BEI GEBRAUCH VON ETOMIDAT

ZUSAMMENFASSUNG

Die Einleitungseigenschaften von Etomidat, einem neuen, intravenös anwendbaren Hypnotikums, wurden bei 400 Patienten beobachtet. Zweihundert Patienten wurden Atropin als Basisnarkotikum verabreicht und mit 0,2, 0,25, 0,3 oder 0,35 mg/kg Etomidat narkotisiert. Der Rest der Gruppe erhielt eines der vier gebräuchlichen Mittel, mit darauffolgender 0,3 mg/kg-Verabreichung von Etomidat. Unwillkürliche Muskelbewegungen waren in mehr als 60% der nur mit Atropin behandelten Patienten vorhanden. Obwohl die Häufigkeit in der zweiten Gruppe herabsank, erwies sie sich bei über 8% als unannehmbar. Andere Reizerscheinungen, sowie Husten und Schluckauf kamen bei ungefähr 10% der Fälle vor. Die kardiovaskulären Veränderungen waren minimal, sowie auch keinerlei ernste allergische Erscheinungen auftraten. Nach-chirurgische Übelkeit und Erbrechen bei bis zu 30% ergaben sich als unzusammenhägend zur Etomidat-Dosierung oder Basisnarkose. Bis 80% der Patienten empfanden die Injektion als schmerzlich, wenn das Mittel in die kleinen peripheren Venen injiziert worden war, so wie sich auch bei Injektion der proximalen Venen, bei 7% Schmerzen ergaben.

EFECTOS DE LAS DOSIS Y PREMEDICACION SOBRE LAS COMPLICACIONES DE LA INDUCCION CON ETOMIDATO

SUMARIO

Se estudiaron en 400 pacientes las características de inducción del etomidato, un nuevo agente hipnótico. Doscientos fueron premedicados con atropina y se provocó la anestesia con 0,2, 0,25, 0,3 ó 0,35 mg/kg de etomidato. El resto recibió una de cuatro premedicaciones normales y se provocó la anestesia con 0,3 mg/kg de etomidato. Se produjeron movimientos musculares involuntarios en más

del 60% de pacientes que recibieron sólo atropina. La frecuencia se redujo en el segundo grupo, pero permaneció inaceptable en más del 8% de los pacientes. La incidencia de otros fenómenos excitables, tales como la tos y el hipo fué aproximadamente del 10%. Los cambios cardiovasculares fueron mínimos y no se observaron fenómenos alérgicos. Se produjeron naúseas y vómitos después de intervención quirúrgica en hasta el 30% de los pacientes. Se observó dolor en la inyección en hasta 80% de los pacientes cuando se inyectó la droga en pequeñas venas periféricas y se produjo en más del 7% cuando se usaron mas venas proximales.