Hospital Topics

Controlled Sedation with Alphaxalone-Alphadolone

M. A. E. RAMSAY, T. M. SAVEGE, B. R. J. SIMPSON, R. GOODWIN

British Medical Journal, 1974, 2, 656-659

Summary

Alphaxalone-alphadolone (Althesin), diluted and administered as a controlled infusion, was used as a sedative for 30 patients in an intensive therapy unit. This technique allowed rapid and accurate control of the level of sedation. It had three particularly useful applications: it provided "light sleep," allowed rapid variation in the level of sedation, and enabled repeated assessment of the central nervous system.

Sedation was satisfactory for 86% of the total time, and no serious complications were attributed to the use of the drug. Furthermore, though alphaxalone-alphadolone was given for periods up to 20 days there was no evidence of tachyphylaxis or delay in recovery time.

Introduction

Many patients needing intensive therapy are acutely aware of their environment, continuously disturbed as a result of nursing care and 24-hour monitoring, and distressed by the discomfort of various indwelling catheters and tubes. In such circumstances potent narcotic analgesic drugs are sometimes given for their euphoric and sedative effects to patients not suffering from severe pain. Alternatively sedative drugs are given to reduce awareness and induce amnesia.

Adequate tranquillity can be achieved, however, only by doses sufficiently large to obtund the level of consciousness. As the breakdown and excretion of currently available sedative drugs is slow[1 2] patients may remain unconscious for unacceptably long periods of time. As a result it is impossible to assess the mental state of many of these critically ill patients, and deterioration of their level of cerebral activity could occur unnoticed.

We report the use of the intravenous infusion of alphaxalone-alphadolone (Althesin), controlled by a constant infusion pump, for the maintenance of "light sleep" in intensive therapy, as described by Savege.[3] Its advantages are that it improves the quality of sedation and because it has a short duration of action the level of consciousness is easily controlled.

Division of Anaesthesia, The London Hospital, London E1 1BB
M. A. E. RAMSAY, M.B., F.F.A. R.C.S., Senior Registrar
T. M. SAVEGE, M.B., F.F.A. R.C.S., Senior Lecturer
B. R. J. SIMPSON, D.PHIL, F.F.A. R.C.S., Professor
R. GOODWIN, B.SC., Technician

Method

Thirty patients were selected on the sole ground that controlled sedation was required. They were all being treated in the intensive therapy unit, where continuous monitoring of vital signs could be undertaken by nurses at the bedside. The only patients excluded were those with gross hepatic failure. The following technique was used: a separate infusion was set up containing alphaxalone-alphadolone. A burette was included in the infusion set and 5 ml of the drug was added to 25 ml of 5% dextrose. The maximum dose of alphaxalone-alphadolone that could be given was thus 5 ml. The concentration of alphaxalone-alphadolone was increased if a restricted fluid intake required this. The infusion rate was controlled by an Ivac infusion pump. Occasionally it was necessary to give 2 ml undiluted alphaxalone-alphadolone to gain initial control in very restless patients. Six levels of sedation were formulated; three with the patient awake and three with the patient asleep.

Awake levels were: 1, patient anxious and agitated or restless or both; 2, patient co-operative, orientated, and tranquil; 3, patient responds to commands only. Asleep levels were dependent on the patient's response to a light glabellar tap or loud auditory stimulus: Level 4, a brisk response; 5, a sluggish response; and 6, no response.

Alphaxolone-alphadolone was prescribed to sedate the patient at one of the above levels, usually between 2 and 4, and the rate of infusion was altered by the nurse to maintain that level. The quality of sedation was assessed by the nurse every five minutes until the desired level was obtained; thereafter assessments were made half hourly. Recovery was evaluated clinically and was taken as the time from discontinuing the infusion until the patient's mental state had apparently returned to the pre-sedation level.

During the pilot study after the first hour of sedation the alphaxalone-alphadolone infusion was stopped and the time taken for recovery noted. Then the alphaxalone-alphadolone infusion was restarted. Otherwise sedation was only stopped when a clinical assessment of the central nervous system was necessary. Continuous electrocardiographic monitoring was maintained throughout. Blood pressure, central venous pressure, and respiratory rate were measured every 5-10 minutes, and then half-hourly as stable maintenance levels were obtained. Electroencephalograms (E.E.G.s) were made on six patients. Haemoglobin, packed cell volume, white cell count, serum urea, and electrolyte levels were measured daily. Liver function tests were performed every third day. Arterial blood gas analysis was performed when indicated.

Tests of significance were applied to mean changes in blood pressure, heart rate, and central venous pressure after the start of the infusion, using Student's t test for correlated means.

Results

Details of the 30 patients included in the study together with the concentrations and total amount of alphaxalone-alphadolone

used are shown in table I. The mean dose of undiluted alphaxalone-alphadolone was 0·079 ml/kg/hr (S.E. of mean ±0·009), and the mean total dose was 635 ml (S.E. of mean ±184); one patient received a total of 4,367 ml of undiluted alphaxalone-alphadolone.

TABLE I—*Details of Patients Included in Trial*

Case No.	Age and Sex	Weight (kg)	Diagnosis	Mean Dose of Alphaxalone-Alphadolone (ml/kg/hr)	Total Dose of Alphaxalone-Alphadolone (ml undiluted)
1	60 M.	72	Post-cardiac surgery	0·0227	139
2	71 M.	65	Acute respiratory failure	0·0187	10
3	54 M.	68	Post-aortic graft	0·0792	70
4	61 M.	80	Post-cardiac surgery	0·0365	35
5	57 M.	80	Crushed chest	0·1138	1,900
6	46 M.	80	Acute respiratory failure	0·0516	550
7	56 M.	70	Head injury	0·1025	131
8	47 F.	50	Myocardial infarction	0·0495	225
9	53 F.	60	Post-cardiac surgery	0·1214	102
10	46 M.	82	Crushed chest	0·0795	1,689
11	47 M.	57	Myaesthenia gravis	0·1170	20
12	64 M.	76	Post-lung surgery	0·0640	343
13	60 F.	54	Post-cardiac surgery	0·0444	3
14	43 F.	55	Myaesthenia gravis	0·2339	4,367
15	58 F.	58	Post-cardiac surgery	0·0345	30
16	50 F.	75	Head injury	0·0216	110
17	75 F.	57	Acute respiratory failure	0·0385	62
18	8 M.	22	Post-cardiac surgery	0·0916	45
19	69 M.	66	Post-cardiac surgery	0·0331	65
20	21 M.	76	Post-cardiac arrest	0·0562	284
21	61 M.	80	Crushed chest	0·0611	330
22	53 M.	79	Multiple injuries	0·0532	800
23	43 M.	74	Post-cardiac surgery	0·0595	76
24	41 F.	67	Post-cardiac surgery	0·1194	4
25	51 M.	83	Postoperative renal failure	0·0836	1,032
26	51 M.	85	Post-biliary surgery	0·0772	3,150
27	50 M.	78	Crushed chest	0·1426	1,335
28	62 F.	52	Post-cardiac surgery	0·2073	1,207
29	39 M.	70	Abdominal trauma	0·0680	400
30	19 M.	75	Head injury	0·0764	550

SEDATION

The mean time spent under sedation was 93 hours (range 1·5-480 hours). One patient was continuously sedated for 20 days.

The quality of sedation was determined by comparing the overall period of acceptable sedation—between levels 2 and 5—with the total infusion period. Sedation was satisfactory for 2,425 hours out of a possible total of 2,803 hours (86·5%; fig. 1). Conscious patients sedated with alphaxalone-alphadolone described that they felt drowsy and mentally relaxed.

The mean time taken to sedate adequately the patients was 9 minutes (S.E. of mean ±2·63). This included longer times with the first patients, but as experience in the technique increased this time became shorter.

The mean time taken for recovery from alphaxalone-alphadolone was 12 minutes (S.E. of mean ±1·36). A change in the level of sedation when alphaxalone-alphadolone was stopped in one patient (case 7) so that a neurological examination could take place is shown in fig. 2. This was possible in 12 minutes.

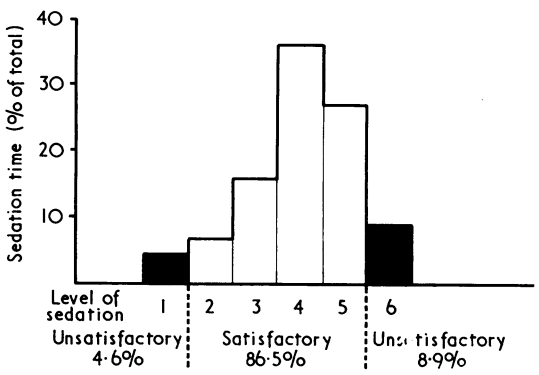

FIG. 1—Time spent at different sedation levels expressed as percentage of total sedation time (see text for definition of sedation levels).

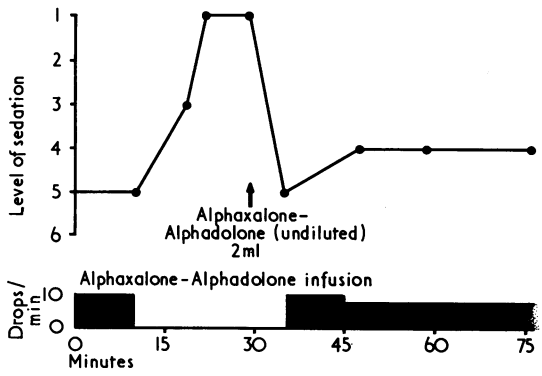

FIG. 2—Change in level of sedation in one patient (case 7) associated with variation in dose of alphaxalone-alphadolone (see text for definition of sedation levels).

OTHER EFFECTS

Cardiovascular Effects.—There were no statistically significant changes in blood pressure or central venous pressure when the patients were sedated with alphaxalone-alphadolone. The initial rise in heart rate, however, was significant ($P < 0·05$; table II).

TABLE II—*Mean (± S.E. of Mean) Changes in Blood Pressure, Heart Rate, and Central Venous Pressure (C.V.P.) after Induction of Sedation with Alphaxalone-Alphadolone*

	Baseline	During Sedation		
		5 min	15 min	30 min
Systolic blood pressure (mm Hg)	128 ± 4·9	131 ± 5	133 ± 4·9	130 ± 5·1
Diastolic blood pressure (mm Hg)	82 ± 3·2	80 ± 3·2	81 ± 3·4	80 ± 3·4
Heart rate (beats/min)	95 ± 3·7	100‡ ± 4·5	99 ± 4·8	99 ± 4·5
C.V.P.* (cm H_2O)	11 ± 0·9	12 ± 1·3	12 ± 1·2	12 ± 1·2

*Results are mean values of 20 patients.
‡ <0·05.

Respiratory Effects.—Nineteen patients were sedated while undergoing intermittent positive pressure ventilation (I.P.P.V.) therefore no change in respiratory pattern could be noted. Seven patients had periods of I.P.P.V. and spontaneous ventilation, and four patients breathed spontaneously throughout. There was no clinical evidence to suggest that alphaxalone-alphadolone depressed ventilation. $Paco_2$ was measured at least daily in patients breathing spontaneously. Of 25 measurements five were above 45 mm Hg. The three patients with raised $Paco_2$ values had pulmonary abnormalities. One developed a pneumothorax several days after a pneumonectomy, one had persistent pulmonary oedema after an emergency mitral valve replacement, and the third had septicaemia complicated by pulmonary oedema. There were never any clinical signs of upper respiratory tract obstruction, but non-intubated patients were not sedated below level 3.

Side Effects.—No side effects were sufficiently serious to justify stopping the alphaxalone-alphadolone, and none lasted over 30 minutes or needed treatment. There were 13 episodes of muscle twitches, 10 of hiccup, eight of nausea, five of salivation, and two of flushed skin. There were no complications at the site of infusion and no evidence of inflammation or phlebitis.

Tachyphylaxis.—There was no evidence that the dose of alphaxalone-alphadolone had to be progressively increased (table III). There were, however, large individual changes in the daily dose requirements. Obviously these were influenced by other factors such as changes in the patient's clinical condition and the use of analgesic drugs, which also have some sedative action.

Additional Drugs.—Alphaxalone-alphadolone was used solely as a sedative; therefore analgesics and muscle relaxants were

given as necessary. Clinically it seemed that less of these agents were needed during the sedation period. Calculation of the doses of these drugs given before, during, and after sedation bears out this impression, but it may be misleading in that the patient's condition is constantly changing and so, therefore, is the drug requirement.

TABLE III—*Mean Change in Daily Dose of Undiluted Alphaxalone-Alphadolone over Seven Days*

Day:	2	3	4	5	6	7
Mean change (±S.D.) (ml)	+5±47	−6±45	−6±36	−9±66	+13±64	−18±39
No. of patients	19	17	12	11	6	6

LIVER FUNCTION

Because alphaxalone-alphadolone is metabolized in the liver serial liver function tests were undertaken to establish, firstly, whether long term infusion lead to liver dysfunction, and secondly, to obtain some estimate of whether patients with liver dysfunction were unable to metabolize alphaxalone-alphadolone efficiently, as evidenced by reduction in required dosage or prolongation of recovery time. The mean alphaxalone-alphadolone requirement (0·073 ml/kg/hr) of the three patients who developed liver dysfunction was slightly lower than that of the whole group (0·079 ml/kg/hr). The abnormal liver function test results of these three patients were, however, readily explicable on other clinical grounds.

Case 1.—This was a patient who underwent heart valve surgery (table IV). He had a stormy operative course with short periods of poor perfusion, severe haemorrhage, and prolonged cardiac bypass. Postoperatively he continued to bleed and needed massive transfusions—over 50 units of blood.

TABLE IV—*Results of Liver Function Tests in Postcardiac Surgery Patient (Case 1) and Patient with Multiple Injuries (Case 22) undergoing Alphaxalone-Alphadolone Sedation*

Case No.	Date	Total Bilirubin (mg/100 ml)	Direct Bilirubin (mg/100 ml)	Alkaline Phosphatase (K.A. units/100 ml)
1*	1/11/72	2·0	1·1	4·6
	6/11/72	10·2	10·0	8·4
	9/11/72	22·4	16·4	10·5
	13/11/72	18·0	12·0	19·0
22†	19/3/73	6·0		11·0
	20/3/73	14·0		11·2
	22/3/73	29·2	21·0	13·8
	25/3/73	37·2		21·8

*Patient received total of 139 ml Althesin from 4/11/72-14/11/72
†Patient received total of 800 ml Althesin from 17/3/73-22/3/73.

Case 22.—This patient with multiple injuries (table IV) had had a period of severe hypotension—four hours with a systolic blood pressure less than 90 mm Hg—and a short period of unrecordable blood pressure. He needed over 30 units of blood during the subsequent 24 hours.

Case 27.—This patient had a severe crushed chest injury. Four days after the cessation of the alphaxalone-alphadolone infusion he developed a Gram-negative septicaemia, became hypotensive, and needed an infusion of noradrenaline and phentolamine to maintain a blood pressure above 90 mm Hg. At the same time he became jaundiced—the total serum bilirubin rose to 12·8 mg/100 ml.

Four other patients showed slight changes in their liver function values (maximum total bilirubin 2·9 mg/100 ml). These changes were not unexpected after the clinical course of their illnesses and were of short duration. The three patients who underwent the longest period of sedation remained with liver function test results within the normal range (table V).

ELECTROENCEPHALOGRAPHY

In the six patients who had E.E.G. recordings made the changes were similar to those seen after induction of anaesthesia with alphaxalone-alphadolone.[4] Five patients were clinically assessed as being between levels 3 to 4. Their E.E.G. changes showed a mixture of fast theta and delta activity; cerebral activity was blocked in response to auditory stimulation. An independent assessor of the E.E.G.s reported that these patients were "lightly asleep." The sixth patient was sedated at level 5, and the E.E.G. showed established burst suppression. In contrast to the other five this suggested a deeper level of anaesthesia. It was particularly noticeable in these six patients that the E.E.G. was consistent throughout the period of the recording, and there was little variation in the level of cerebral activity.

Discussion

Alphaxalone-alphadolone diluted as an infusion has been shown to provide satisfactory sedation in a wide variety of patients. This was rapidly achieved in every case and, with practice, easily maintained at the desired level for as long as necessary. Recovery from the effects of alphaxalone-alphadolone was also rapid, at a mean time of 12 minutes, and was not significantly prolonged in patients who had received a large dose over several days. This lack of cumulative effect is probably due to the short plasma half life of alphaxalone-alphadolone, and its rapid excretion, which has been shown in animals,[5] compared with the delayed elimination of other sedative agents.[1 2]

Alphaxalone-alphadolone sedation has three particularly useful applications. Firstly, it provides light sleep. Some ill patients are very aware of their surroundings and are not only uncomfortable because of various indwelling catheters and tubes but are also continuously disturbed as a result of 24-hour monitoring and nursing care. "Tranquillizers" are often inadequate for this group. After some days of intensive therapy such patients show signs of mental and physical exhaustion. This problem has been overcome by the use of alphaxalone-alphadolone to induce a state of "light sleep" from which they can be easily and readily wakened if necessary. Furthermore, it is possible not only to wean patients off the ventilator but also to extubate them without their being aware of this uncomfortable sequence.

Secondly, it provides rapid variation in the level of sedation. Some patients need rapidly varying levels of sedation as part of their management. For example, during weaning from a ventilator the patient will often need heavy sedation during ventilation yet must be awake and co-operative when breathing spontaneously.

Thirdly, alphaxalone-alphadolone allows repeated assessment of the central nervous system. Long-acting sedative drugs are

TABLE V—*Results of Liver Function Tests in Three Patients who underwent Longest Periods of Sedation*

	Case 5			Case 10			Case 14		
	1/12/72	6/12/72	18/12/72	25/1/73	29/1/73	7/2/73	1/3/73	7/3/73	20/3/73
Total serum bilirubin (mg/100 ml)	1·2	1·2	0·3	1·2	0·3	0·3	0·2	0·3	0·2
Direct bilirubin (mg/100 ml)	0·8	0·4	0·0	0·6	0·0	0·0	0·0	0·0	0·0
Alkaline phosphatase (K.A. units/100 ml)	14·6	15·9	19·9	5·8	5·4	7·2	7·1	10·7	8·0
Total alphaxalone-alphadolone infused (undiluted)	1,900 ml			1,689 ml			4,367 ml		

contraindicated in patients with acute neurological disorders as they may mask changes in the cerebral state and preclude neurological assessment. Their use may become mandatory, however, if the patient becomes uncontrollable. Alphaxalone-alphadolone has allowed "finger tip" control of sedation that has never failed to produce the desired effects, and yet allows rapid smooth recovery for neurological examination. Its use has three additional advantages in this group of patients. Firstly, in the doses used in this series it did not prevent the pupillary reaction to light. Secondly, when moderate hypothermia was used alphaxalone-alphadolone reduced shivering and promoted peripheral vasodilatation. Finally, studies have shown that cerebral oxygen consumption, intracranial pressure, and cerebral blood flow are considerably reduced, albeit in the undamaged brain.[6 7]

LIMITATIONS OF TECHNIQUE

Alphaxalone-alphadolone in subanaesthetic doses does not relieve somatic pain[8 9] and should not be given in place of analgesic drugs. As with most other potent central nervous system depressants alphaxalone-alphodolone does have some cardiorespiratory depressant effects,[10] which are likely to be more definite in shocked patients, and considerable caution would be needed if this technique was used in such subjects.

Of the 11 patients who were sedated while breathing spontaneously three were unable to breathe adequately and had to be reventilated. In each patient the respiratory failure which occurred could be explained on clinical grounds, but possibly alphaxalone-alphadolone contributed to it. The problems inherent in sedating patients suffering from acute respiratory failure are acknowledged, but these patients could not have been managed without some form of sedation. The danger was minimized since each patient was continuously observed. All sedative drugs in adequate dosage are likely to have depressant actions. Further studies into the effects of alphaxalone-alphadolone on the CO_2 response curve in fit volunteers and in patients with respiratory disease will be reported separately.

Clearly, alphaxalone-alphadolone should be given only as an infusion where there is reliable continuous supervision, adequate monitoring facilities, and where some safety precautions, such as the use of an infusion pump, are taken to ensure that accidental gross overdosage does not occur.

Sedation was unsatisfactory for some 14% of the time. A small proportion of this was unavoidable in that it was precipitated by the need for neurological examinations. Patients were too lightly or too deeply sedated for two main reasons, both of which are avoidable. Firstly, administration of a bolus induction dose (1-2 ml undiluted alphaxalone-alphadolone in adults) could have overcome the delay between starting the infusion and achieving a satisfactory level. Secondly, it took time for nurses to learn the technique of altering the infusion rate to achieve the required level of sedation. No patient came to harm and reversal to a satisfactory level was easily and rapidly achieved by stopping the infusion. Furthermore, no patient showed appreciable respiratory or cardiovascular depression. No major complications were seen in this series though hiccup and involuntary muscle movement did occur occasionally. Vomiting was never noted.

In conclusion, a continuous infusion of dilute alphaxalone-alphadolone provides a wide and controllable range of sedation that can be easily and rapidly varied. It was particularly valuable in patients who needed intermittent periods of controlled ventilation; in restless and confused patients, especially those with cerebral trauma; and in patients in whom large doses of conventional sedatives failed to be effective. It should be used, however, only where continuous supervision and adequate monitoring facilities are available.

We thank Dr. Donald F. Scott, Department of Electroencephalography for the interpretation of electroencephalograms.

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Conversations on the Social Services

City Problems

Dr. M works with his partners in a Greater London practice, which he describes.

FROM A SPECIAL CORRESPONDENT

British Medical Journal, 1974, 2, 659-660

"Most of the patients in the immediate surroundings of the practice belong to social classes 4 and 5, and they are very mixed racially. Roughly a third are immigrants from the West Indies, some from India and other parts of the world, about 15% Irish—so that only half the practice are English. We have an enormous turnover, around a third of the practice a year, and a host of temporaries. There is a considerable number of people in social classes 1, 2, and 3 who are newly-married, have the first child here, and move on somewhere better. The ones who stay are the ones left behind in the rat race. And then we get quite a few who come in from the wealthier parts around, so we have some who arrive in Rolls Royces. The one group that is missing is the skilled artisan, living in his own house with a garden. The sort of social problems they have are due to low income, being an immigrant in an alien culture, being unmarried and lonely, being old and lonely, inadequate accommodation or play facilities, inadequate cultural facilities for the more intelligent children in a basically low level educational area.

"People in all ranges of society have problems, and one of the biggest is the idea engendered by the medical profession