TOWARDS A STANDARDIZED ANAESTHETIC STATE USING ISOFLURANE AND MORPHINE

H. M. ROBB, A. J. ASBURY, W. M. GRAY AND D. A. LINKENS

SUMMARY
In 34 patients undergoing major surgery, the inspired isoflurane concentration was adjusted by a control system designed to maintain systolic arterial pressure at a predetermined value. An empirical rule allowed additional morphine administration if the demand of the system for isoflurane was excessive. Satisfactory control of systolic arterial pressure was achieved in 31 patients and the anaesthetic state was clinically acceptable to an independent observer; no awareness was reported and the mean recovery time was 9.6 min. In these patients, control of systolic arterial pressure produced a pattern of clinical signs recognizable as general anaesthesia. (Br. J. Anaesth. 1993; 71: 366-369)

KEY WORDS

Despite obvious shortcomings, clinical signs are the only practical, widely accepted method of determining adequacy of anaesthesia. Although using these signs results in an acceptable anaesthetic state in most patients receiving general anaesthesia, because their interpretation is subjective there is no clinical standard of anaesthesia against which new methods of assessing anaesthetic “depth” might be compared.

We have shown that a simple control system designed to maintain systolic arterial pressure (SAP) at a predetermined value by adjusting the inspired concentration of enflurane produces a clinically acceptable state of anaesthesia [1]. This suggests that SAP is a major component in the clinical assessment of the anaesthetic state.

The objective of this study was to determine if a clinically acceptable anaesthetic state could be achieved by altering isoflurane dosage to maintain SAP at a predetermined value.

PATIENTS AND METHODS
We studied 34 ASA I and II patients admitted for elective major gynaecological surgery. Local Ethics Committee approval was obtained and all patients gave written, informed consent. Patients with cardiovascular disease and those taking drugs acting on the central nervous system (except sleeping tablets) were excluded.

Patients were premedicated with ranitidine 150 mg and temazepam 10–20 mg. Anaesthesia was induced with morphine 0.1 mg kg⁻¹ and thiopentone 2.5 mg kg⁻¹. Additional thiopentone was given if the eyelid reflex was not abolished. Vecuronium 0.1 mg kg⁻¹ was given and the patient’s lungs ventilated with 70 % nitrous oxide in oxygen supplemented with 1 % isoflurane. The trachea was intubated and the lungs ventilated using a Bain system with a fresh gas flow of 70 %, nitrous oxide in oxygen 100 ml kg⁻¹ min⁻¹. Carbon dioxide monitoring was not available and the fresh gas flow used was intended to maintain moderate hypocapnia [2]. Isoflurane was delivered by a Fortec 3 vaporizer (Cyprane), modified to allow it to be driven by computer control. Additional boluses of morphine were given on instruction from the program. Neuromuscular block was maintained with increments of vecuronium at 30-min intervals. The patients received Ringer’s lactate solution 1 litre over the first 1 h and 500 ml every subsequent 1 h. Blood loss was replaced with extra crystalloid, colloid or blood products as indicated.

Anaesthetic adequacy was assessed clinically according to normal practice, and at 5-min intervals, using the FRST (arterial Pressure, heart Rate, Sweating, lachrymation (Tears)) score [3]. Automatic control was discontinued approximately 5 min from the end of surgery, and the nitrous oxide discontinued after the last skin suture. Any residual neuromuscular block was antagonized with neostigmine and glycopyrronium. Before tracheal extubation, patients who had not received additional morphine were given a bolus dose of 0.05 mg kg⁻¹.

Recovery was considered complete when the patient was able to respond to a request to open the eyes or protrude the tongue.

A consultant anaesthetist, not involved with the study, checked that the anaesthetic dose administered by the system was appropriate. Patients were interviewed the next day to establish if they had been aware during surgery.

During the early part of the study, three patients developed bradycardia (about 50 beat min⁻¹). These
incidents were managed by temporarily stopping surgery and injecting atropine. The regimen was modified so that any other patient developing a heart rate of less than 50 beat min\(^{-1}\) during surgery would be given 0.2-mg increments of glycopyrronium until the rate was greater than 60 beat min\(^{-1}\).

**Equipment**

The equipment and its inherent safety features have been described in detail elsewhere [1, 4]. In summary, a proportional-plus-integral (PI) control algorithm was implemented on a computer interfaced to a Critikon 1846 Dinamap and a vaporizer controller [4]. The vaporizer and controller were checked against a Datex Normac analyzer before each case. The program was designed to maintain the patient's SAP at a target value (TSAP), which was 90% of the SAP predicted from age and sex standardized tables [5]. SAP was measured at 1-min intervals and appropriate adjustments in inspired isoflurane concentration made automatically. The vaporizer setting was determined by the following rule:

\[
\text{Isoflurane concentration } (\%) = K_p e + K_i (\sum e + I_o),
\]

where \(e\) = difference between the actual systolic arterial pressure and the target systolic arterial pressure (SAP-TSAP); \(K_p\) and \(K_i\) = proportional and integral gains; \(I_o\) = a preloaded value for the integral, included to shorten the stabilization time.

The gain settings used in the earlier enflurane study were retained to allow comparison [1], \(K_p\) being set to 0.1% (mm Hg\(^{-1}\)), \(K_i\) to 0.01% (mm Hg\(^{-1}\)) and \(I_o\) to [120-(age in yr)] mm Hg. The sum of \(e\) was set to zero at the beginning of each case, and reset to zero when morphine increments were given.

Two additional rules were incorporated in the control algorithm: first, a minimum concentration of 0.6% isoflurane was delivered for the first 10 min, to avoid the risk of inadequate dosing and consequent awareness at the time of the initial surgical incision (if SAP was less than TSAP subsequent to induction); second, if the sum of five consecutive vaporizer settings exceeded 15%, the controller requested the anesthetist to give an increment of morphine 0.05 mg kg\(^{-1}\). In addition, the integral term was automatically reset to its preloaded value. This arrangement could be activated only at 15-min intervals. The last rule was designed to mimic the anesthetist's response to a patient who requires large doses of volatile agent.

**Statistics**

The root mean square deviation (RMSD) of the SAP measurements around the TSAP was used to assess the quality of SAP control. Calculation of the RMSD is analogous to that for standard deviation, but uses the TSAP in place of the mean. Recovery times were recorded, as they could indicate a relative anaesthetic overdose, particularly towards the end of the procedure.

The requirement for additional morphine or anticholinergic agent was used to classify the patients into three groups, as described in the results section.

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**Table 1. The surgery performed. Group A received neither additional morphine nor an anticholinergic agent. Group B received additional morphine alone and group C an anticholinergic agent alone.**

<table>
<thead>
<tr>
<th>Operation</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy and salpingo-oophorectomy</td>
<td>A 13</td>
</tr>
<tr>
<td>Ovarian cystectomy</td>
<td>B 2</td>
</tr>
<tr>
<td>Vaginal hysterecctomy, pelvic floor repair</td>
<td>C</td>
</tr>
<tr>
<td>Reversal of sterilization</td>
<td></td>
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<tr>
<td>Bilateral salpingo-oophorectomy</td>
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### RESULTS

Details of the procedures are listed in table I and an example of the progress of automatic control is shown in figure 1. Adequate control of SAP was not achieved in one patient, despite additional morphine, and a breach of procedure occurred in two others: one did not receive an increment of morphine on time and the second suffered a sudden 3.5-litre blood loss, resulting in an SAP less than TSAP for 50 min. Results from these three patients were excluded from analysis.

The remaining patients were classified into groups on the basis of their responses under anaesthesia with the control system. Group A (16 patients) received morphine at induction only, while group B (five patients) required one additional dose of morphine. No patient required more than one dose of morphine. Group C (10 patients) received an anticholinergic agent to treat bradycardia. No patient who received an anticholinergic agent required additional morphine.

No patient complained of awareness when questioned after operation. The anaesthetic state was acceptable to the supervising independent anaesthetist in all cases. This is reflected by the mean PRST score of 0.9. In addition, SAP (mean 118.2 (SD 6.6) mm Hg), heart rate (mean 78.3 (10.5) beat min\(^{-1}\)) and rate–pressure product (mean 9246 (1326) mm Hg min\(^{-1}\)) were acceptable. The mean recovery time was 9.7 (7.8) min. All patients indicated that they would accept the same anaesthetic again.
isoflurane concentration were significantly smaller in group A than in group B. Of these, only the required dose of isoflurane was greater in group B than in group C. There was no difference in heart rate, rate-pressure product or isoflurane requirement between groups A and C. The patients in group B took significantly longer to recover than those in the other groups.

Sweating was not observed in those patients who received an anticholinergic agent, but was observed in the two other groups. The association between sweating and administration of anticholinergic agent was statistically significant.

**DISCUSSION**

The control system achieved the objective of maintaining systolic arterial pressure at its target and this resulted in a clinically acceptable pattern of clinical signs, supporting our view that SAP is a major component of the clinical assessment of the anaesthetic state.

The differences between groups A and B may be explained by the rule that gave rise to the additional morphine doses. The greater isoflurane (and morphine) requirement in group B is an obvious example. Other differences such as the greater heart rate in group B may reflect either increased autonomic activity or an effect related to the larger doses of isoflurane these patients received. Despite these differences, anaesthesia was clinically acceptable in both groups.

The only significant difference between groups A and C was the greater heart rate in group C. Otherwise, groups A and C were similar. Moderate doses of anticholinergic agents did not appear to detract from the usefulness of SAP as an indicator of anaesthetic adequacy. Further studies, in which some patients would receive an anticholinergic agent at induction of anaesthesia, are required to confirm this finding.

No patient in our previous study with enflurane had bradycardia sufficient to require treatment [1], but three patients in this study required rapid treatment for bradycardia. We do not know why bradycardia might occur more frequently in patients anaesthetized with isoflurane, but it may be simply a surgical effect of peritoneal traction.

The PRST score is a simple method of measuring the clinical adequacy of anaesthesia [3]. The greater
mean PRST scores in those patients who required morphine or received an anticholinergic agent reflected the greater heart rates in these groups. This probably represents a pharmacological effect rather than an increase in autonomic activity.

Our observation that sweating was absent in patients who received anticholinergic drugs is not surprising, and suggests that anticholinergic agents might limit the usefulness of sweating as a sign of inadequate anaesthesia. The PRST score, which includes a score for sweating, must be interpreted with care under these circumstances.

Although the use of clinical signs (SAP in this case) to guide anaesthetic dosage may be criticized [6, 7], these signs are used widely in current anaesthetic practice and it is therefore highly likely that they carry useful information. Obviously, the usefulness of clinical signs may be reduced by drugs such as beta-blockers, conditions such as hypertension or intraoperative "events" such as surgical haemorrhage. The system we have described would be of limited routine clinical use in these situations. However, a standardized anaesthetic state, used under controlled circumstances, would be useful in evaluating the newer techniques (such as monitoring evoked potentials) proposed to assess the anaesthetic state [8].

As anaesthetists use combinations of clinical signs and anaesthetic agents to achieve an anaesthetic state, our single input (SAP), single output (iso-flurane) system has obvious limitations. However, if the control system can be developed to use additional clinical signs, the clinical anaesthetic state will be defined objectively by the algorithm on which the system is based. Several factors must be considered before addition of other clinical signs: many signs (e.g. tears) are subjective; the measurement of some is difficult to automate (e.g. pupil diameter [9]); the value of others might be limited (e.g. sweating); finally, weighting must be applied to each additional sign.

We chose SAP as a starting point as it is an easily measured objective sign with a well established range of acceptable values. In our system, the target systolic pressure (TSAP) effectively set the depth of anaesthesia. The choice of TSAP was difficult, as single measurements in the ward or anaesthetic room are likely to be unrepresentative of the patient's true resting values because of anxiety or sedation [10]. Our use of tables to determine TSAP overcame the immediate problem, but suffered the disadvantage that it had a population rather than an individual basis. The requirement for additional morphine in our studies probably reflected an inappropriately small TSAP for individual patients rather than a relative resistance to anaesthetic agents; this interpretation is supported by the significantly longer recovery times in those patients who required additional morphine. Repeated measurements in the ward using a non-invasive arterial pressure monitor may give a more realistic value for the TSAP.

A major limitation of control systems is that they cannot predict changes in external circumstances, such as surgical stimulation. In addition, our system was originally designed to control SAP with a single agent, whereas anaesthetists tend to limit the requirement of a volatile agent by use of opioids. We attempted to overcome these problems by the incorporation of the additional rules. As a few patients took a prolonged time to recover from the anaesthetic, despite the additional rules, these may require modification if an individually determined value of TSAP does not overcome this problem.

Building on the pioneering work of Suppan [11], our studies have laid some groundwork for developing a more flexible control system which may mimic more closely the activity of the anaesthetist. We believe that the system requires more patient information in order to give reliable control in a wider range of conditions, and plan to develop it to include additional clinical signs as additional controlled variables.

REFERENCES
7. Hug CC. Lipid solubility, pharmacokinetics, and the EEG: Are you better off today than you were four years ago? Anesthesia 1985; 62: 221-225.