EFFECT OF ARFONAD® ON ANESTHETIC REQUIREMENTS DURING CYCLOPROPANE ANESTHESIA

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CONTROLLED hypotension has wide usage in the anesthetic management of surgical patients. Arfonad® (*d*-3, 4-[1′,3′-dibenzyl-2′-ketoimidazolido]-1, 2-trimethylene thiophanium *d*-camphor sulfonate) has been used extensively for the production of controlled hypotension in our clinic. Clinically, we and others (1) were of the impression that Arfonad reduced the amount of anesthetic agent required to maintain surgical anesthesia during the period of induced hypotension.

To determine whether this clinical impression of decreased requirement of anesthetic agent was true, we undertook a study of this problem by a controlled experiment. Electroencephalographic records can be used to judge the depth of anesthesia (2, 3). Therefore, continuous electroencephalograms were obtained on patients during cyclopropane anesthesia in order to determine if, following the administration of Arfonad, any change in pattern could be observed. A more sensitive indicator of anesthetic requirements, a servo (automatic) anesthetic administrator coupled with a recording potentiometer, was then incorporated into our recording system.

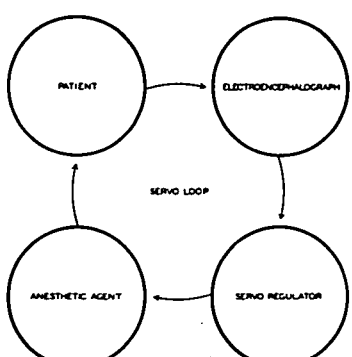

FIG. 1. The servo loop.

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The servo loop first used in anesthesia by Bickford in 1950 (4) consists of a patient, an electroencephalographic recorder, a servo regulator and a means of delivering the anesthetic agent. Feedback exists through each component to complete the loop, as indicated in figure 1. This is the essence of a homeostatic system.

METHOD

Observations were made on 10 normotensive female patients undergoing radical or simple hysterectomy. Premedication consisted of 0.4 mg. of atropine alone or with an appropriate dose of an opiate or barbiturate. Induction was accomplished using cyclopropane-oxygen

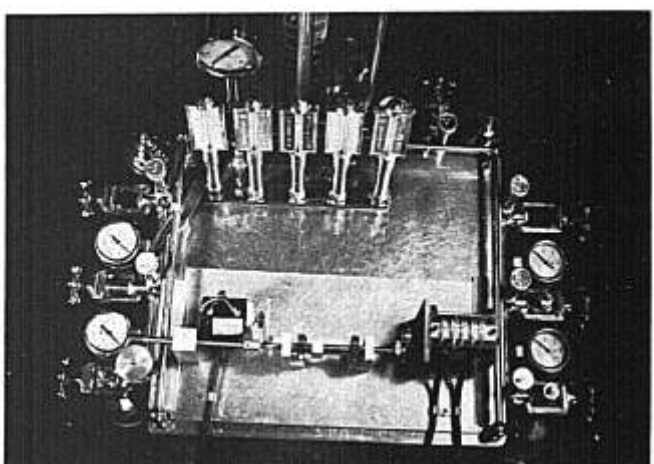

FIG. 2. Heidbrink cabinet Kinet-o-meter with anesthesia servo mechanism.

in a Heidbrink circle carbon dioxide absorber system. A cuffed endotracheal tube was passed to maintain a closed system. Fronto-occipital electroencephalographic needle scalp leads and electrocardiographic limb leads were attached for recording purposes. Recordings were made with a Grass III D electroencephalograph. Cyclopropane anesthesia was deepened until electroencephalographic pattern IV (3), which corresponds to the third plane of surgical anesthesia, was observed and at that time the servo machine was incorporated into the system. Simultaneously the cyclopropane gas flow was recorded by the recording potentiometer which registered the position of the cyclopropane gas flow valve and thus had been previously calibrated to read

cyclopropane gas flow. After at least twenty minutes the system had come to anesthetic equilibrium.

Arfonad was then given by rapid single intravenous doses of from 0.1 to 0.2 mg. per kg. in order to determine its effect on cyclopropane gas flow. This dose usually dropped the blood pressure to 60 to 80 mm. of mercury systolic. During this time the patients were placed supine with the pelvis the highest point, the feet and head lowered in order to attempt to preclude hypostatic cerebral ischemia and to

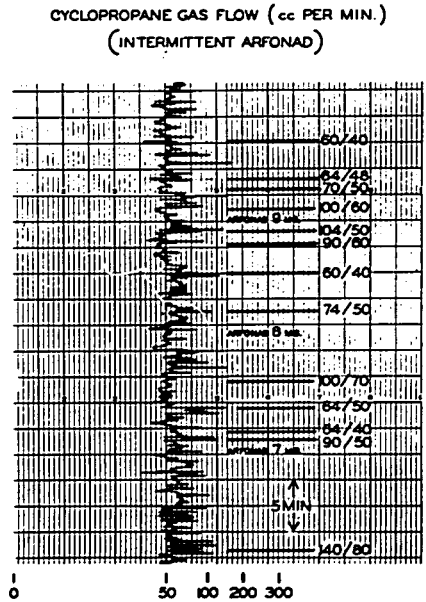

FIG. 3. Cyclopropane gas flow record during challenge with Arfonad. Time progresses from bottom to top.

provides a bloodless operative field. Subsequent similar doses of Arfonad were administered when the blood pressure recovered to a systolic of 100 to 110 mm. of mercury. In order to test the sensitivity of the servo system after discontinuance of Arfonad, at which time the blood pressure always had returned to pre-Arfonad levels, 25 mg. of thiopental sodium was rapidly administered intravenously. All blood pressures were obtained by sphygmomanometic technique. Blood loss was estimated and blood was continuously replaced during the operation to maintain normovolemia.

The servo mechanism used in this study with cyclopropane and Arfonad continuously varies the gas flow by means of a two-phase servo motor in response to the electroencephalographic pattern and maintains a constant level of anesthesia as interpreted by the electroencephalographic recording (fig. 2). The servo motor is driven by a servo amplifier, which consists of a discriminator, integrator, balanced modulator and push-pull power amplifier (5). It must be noted, however, that a servo loop is not a calibrated system and will correct continuously and indiscriminately for all types of disturbances.

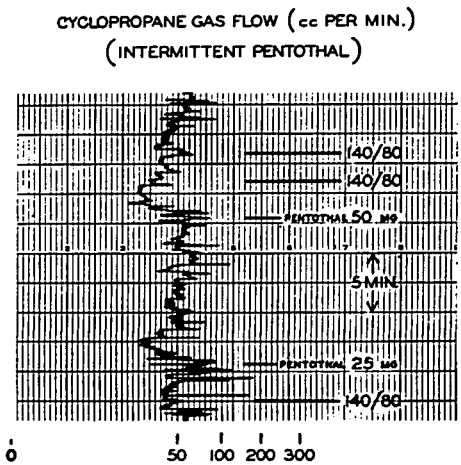

FIG. 4. Cyclopropane gas flow record during test with thiopental sodium. Time progresses from bottom to top.

RESULTS

A total of 55 challenges with arfonad were made in the 10 cases. In not a single one of these challenges were we able to detect any increase or decrease in the cyclopropane required to maintain electroencephalographic pattern IV. Furthermore, Arfonad given in repeated doses over a period of time also did not change the anesthetic requirements. The electroencephalographic pattern remained stable during all of these challenges.

Figure 3 shows a typical gas flow record prior to and during the injection of Arfonad. It shows that the cyclopropane gas flow remained unchanged in spite of hypotension produced by Arfonad. Prior to Arfonad administration, the constant level of anesthesia was maintained with a gas flow of 50 cc. of cyclopropane per minute. This gas flow continued unchanged during single and repeated doses of Arfonad.

Figure 4 shows the effect of 25 and 50 mg. of thiopental sodium administered intravenously to the same patient. The cyclopropane gas flow in both instances was reduced automatically by the servo mechanism. Each system tested in this way indicated a decrease in cyclopropane gas flow following the administration of 25 mg. of thiopental sodium intravenously.

DISCUSSION

In order to determine the anesthetic potentiating effect of agents given to patients who are anesthetized it is necessary to measure and control the level of anesthesia by more accurate means than the subjective impressions of the anesthesiologist. Thus the anesthetic level was measured by the electroencephalogram and maintained constant by the servo mechanism.

To control the level of anesthesia by a servo mechanism the following conditions must be fulfilled: (1) The level of anesthesia must be measurable, (2) the required changes in administered anesthetic must be controlled by some physical means, and (3) both measurement and regulation must be rapid enough to make the system feasible.

For our purposes the anesthetic level is taken to mean the electroencephalographic patterns which accompany different concentrations of arterial blood cyclopropane. Possati, Faulconer, Bickford and Hunter reported that an almost straight line correlation existed between the changes in electroencephalographic pattern and the arterial blood cyclopropane concentration (3). Cyclopropane is a potent, rapid acting agent (6) and experiments performed during the development of the servo machine confirmed the impression that the agent could be automatically controlled.

A flow of about 50 cc. of cyclopropane per minute was usually required to maintain a constant level of anesthesia in these patients. This constant flow of 50 cc. of cyclopropane per minute represents the amount of gas necessary to maintain anesthetic equilibrium by making up for that gas which diffuses through the skin, rubber connections, and also that amount absorbed from the plasma by less saturated tissues.

The effect of several anesthetic agents on the central nervous system as measured by the electroencephalogram is additive. Anoxia and carbon dioxide accumulation also will produce a deeper electroencephalographic pattern when superimposed on a constant level of anesthesia (7, 8).

Cyclopropane was the sole anesthetic agent. Adequate gas exchange was maintained at all times by assisted respiration to preclude hypoxia and hypercapnia. The 10 degree head-down position was employed in an attempt to guard against cerebral hypoxia at hypotensive levels. Arfonad was the only secondary agent introduced into this system.

If Arfonad had an anesthetic action, it should produce a deeper electroencephalographic pattern and the servo mechanism in turn would feed less anesthetic agent to maintain electroencephalographic pattern IV. From our results Arfonad had no effect on the servo cyclopropane gas flow or on the electroencephalographic pattern. Therefore, Arfonad has no appreciable central anesthetic action.

SUMMARY

Patients in the 10 degree head-down position showed no appreciable decrease in cyclopropane requirements during rapidly induced hypotension with Arfonad.

A method by which servo anesthesia can be used to assay possible anesthetic potentiating effects of simultaneously administered agents has been presented.

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