COMPARISON OF THE EFFECT OF DIISOPROPYL PHENOL (ICI 35868) AND THIOPENTONE ON RESPONSE TO SOMATIC PAIN

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SUMMARY

The response to somatic pain with sub-hypnotic doses of ICI 35868 (diisopropyl phenol in cremophor) and thiopentone was compared using tibial pressure algesimetry. Studies were also carried out following recovery from larger doses of both drugs. The patients underwent minor gynaecological procedures using only one of the two i.v. agents and nitrous oxide in oxygen. The studies confirmed the known antanalgesic action of thiopentone and demonstrated that diisopropyl phenol has an analgesic action which is an attractive feature in an i v anaesthetic agent.

It is generally accepted that small doses of thiopentone cause an increased sensitivity to somatic pain (Clutton-Brock, 1960; Dundee and Moore, 1960a). This antanalgesic action adversely influences the use of thiopentone as sole anaesthetic. The ideal i.v. anaesthetic should either have a slight analgesic action or at least not increase sensitivity to pain (Dundee, 1979). For this reason, it is important that evaluation of potential new i.v. anaesthetics should include a study of their effect on somatic pain in man.

This paper reports algesimetry studies with small sub-hypnotic doses of the new i.v. anaesthetic, diisopropyl phenol (Kay and Stephenson, 1980; Rutter et al., 1980) and these are compared with similar studies using thiopentone. It also reports corresponding findings in the period after operation in patients who received large doses of each drug as principal anaesthetic.

METHODS

The studies were carried out in fit unpremedicated women undergoing minor gynaecological operations. There was no choice as to which agent was used except that patients with a history of exposure to cremophor or with known allergy or atopy were not given diisopropyl phenol. The studies were carried out immediately before induction of anaesthesia, the procedure having been explained to the patients and their consent obtained.

Gradually increasing pressure was applied to the skin overlying the anterior surface of the middle third of the tibia using an inverted modified domestic balance with a metal disc of 9.2 mm diameter which had replaced the tray. Patients were asked to identify when the sense of pressure first changed to pain and when the pain became intolerable or they moved their legs in response to the pain. The first reading was taken as the pain "threshold" and the latter termed pain "response". The readings were measured as the gradations on the scales at which the various endpoints appeared. All observations in one patient were carried out by the same observer on one leg either in a quiet area adjoining the operating theatre or in the theatre itself before anaesthesia was induced. The average of the threshold and response readings was used for analysis of the data.

A minimum of two control readings were taken before any drug was injected and if these were within the accepted range of error of the method, the study commenced. Otherwise, a third reading was taken and if the scatter was still excessive, the
patient was excluded from the study. Previous experience (Dundee and Moore, 1960a) has shown that duplicate readings should not vary by more than one unit on the scales. Patients who found the procedure to be distressing and who were unable to concentrate were also excluded.

The study was divided into two parts. In the first, the patient received sub-anaesthetic doses of either of the two drugs under study and algometry readings were taken at 1-min intervals for 3 min after injection. Twenty patients were studied with each of the drugs. With diisopropyl phenol, the initial study in 10 patients was with 0.25 mg kg\(^{-1}\) which was repeated after 3 min. A further 10 patients were given doses of 0.5 mg kg\(^{-1}\). The doses of thiopentone given to the other 20 patients ranged from 0.4 to 1.4 mg kg\(^{-1}\). When the study was completed, the patients were given a full induction dose of one or other of the agents and anaesthesia was carried out in the normal manner. They were not subjected to any further studies.

In the second study, control readings were taken as above, but anaesthesia was induced with normal doses of either diisopropyl phenol 2 mg kg\(^{-1}\) or thiopentone 4 mg kg\(^{-1}\). Anaesthesia was maintained with intermittent doses of the induction agent and nitrous oxide in oxygen, but no other agents were given. Nitrous oxide was discontinued at the end of the operation and the algometry readings repeated as soon as the patients were sufficiently conscious to respond to commands. Repeat readings were carried out at intervals of 2-3 min depending on the results. This investigation was continued until the readings had returned to within the accepted range of variation from the preoperative control. Twenty patients were studied after the large doses of diisopropyl phenol, and 18 after thiopentone.

In presenting data for sub-hypnotic doses, the frequency is given of what are considered to be significant changes from control readings of either analgesia or antanalgesia. It is not considered that this is a sufficiently quantitative method to grade the response other than being indicative of analgesia or antanalgesia (increase or decrease in readings from control). Only a statistical comparison of the frequency of these changes using the \(\chi^2\) analysis has been made.

In the period after operation, the variation from the preoperative control readings of individual patients is shown and results illustrated with typical cases. The results were such that a statistical evaluation was not necessary.

**RESULTS**

Results from patients who received sub-hypnotic doses of the drugs are given in table I, while table II illustrates the results in the 10 patients who were given a second dose of diisopropyl phenol 0.25 mg kg\(^{-1}\). There is a significant difference (\(\chi^2 = 14.08; P<0.001\)) between the responses of the patients to the two drugs. Most of those who received diisopropyl phenol showed either no change or analgesia, while antanalgesia was a feature of patient receiving thiopentone.

The postoperative findings in 20 patients who received an average of diisopropyl phenol 4.1 mg kg\(^{-1}\) with nitrous oxide in oxygen for minor operations is shown in figure 1. Timing was taken from the end of anaesthesia, all patients being awake within 5 min. The figure demonstrates a residual analgesic action persisting for 40-50 min in some patients. A similar study with thiopentone in 18 patients who received doses averaging 6.2 mg kg\(^{-1}\) (fig. 2) shows a mainly antanalgesic effect persisting for up to 300 min.

The difference between the two drugs is more obvious in figures 3 and 4 which show typical findings with each agent in six patients.
FIG. 1 Changes in postoperative pain readings following large doses of diisopropyl phenol compared with preoperative controls. ... = Range of expected normal variations in readings.

FIG. 2 Changes in postoperative pain readings following large doses of thiopentone compared with preoperative controls. ... = Range of expected normal variations in readings.
DISCUSSION

Results with thiopentone are quantitatively and qualitatively similar to those obtained some 20 years ago with the same method (Dundee, 1960) and demonstrate a state of antanalgesia or hyperaesthesia (Keats, 1965). However, this state of increased sensitivity to somatic pain was not a feature of either small sub-hypnotic doses of diisopropyl phenol or of recovery from large full anaesthetic doses. The two drugs behaved differently in both the preinduction and recovery periods and were opposite in their effect on patient appreciation of somatic pain.
RESPONSE TO SOMATIC PAIN

There is no obvious explanation for the difference in response to the two drugs although there have been several attempts made to explain the antanalgesic action of thiopentone (Clutton-Brock, 1960; Brazier, 1961). A transient analgesic action has been demonstrated with propanidid (Dundee and Clarke, 1965), while ketamine is shown to have a more prolonged analgesic action. This latter effect has been attributed to an increase in circulating catecholamines. No comparable data are available for the drugs used in the present study.

These findings agree with the clinical action of the two drugs. Although experience with disopropyl phenol is limited, patients have not been found to react vigorously to stimuli under light anaesthesia as commonly occurs with thiopentone. Undoubtedly, this would make it a more versatile drug for minor procedures in which it could be used as sole agent.

One might suggest cremophor as an agent in inducing analgesia as it is the solvent used for both propanidid and disopropyl phenol. There have been no reports of its analgesic action and this is an unlikely explanation, as the solution of ketamine which has a definite analgesic effect is aqueous.

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REFERENCES


