SUMMARY

During body surface surgery anaesthesia with thiopentone, nitrous oxide-oxygen was accompanied by a small rise in blood sugar whereas when propanidid was substituted for thiopentone there was a much larger rise. A single intravenous dose of both agents in the absence of surgery induced no hyperglycaemia and it is considered that the response is probably related to the stress of surgery and the differing abilities of the two agents to obtund the response.

Blood sugar changes have been studied under a variety of types of premedication, anaesthesia and surgery, and widely differing results have been obtained. Early studies on dogs and other animals indicated that there was a mild hyperglycaemia under thiopentone anaesthesia. Liver glycogen was depleted under long anaesthesia and there was inability to store glucose administered before or during the anaesthetic.

In man most workers have found slight hyperglycaemia during diiopentone anaesthesia, similar to that occurring with cyclopropane and much less than that with diethyl ether. Ether hyperglycaemia is inhibited by induction with thiopentone (Bass, Watts and Chase, 1953). In a detailed analysis Dundee (1956) and Dundee and Todd (1958) showed that in subjects without premedication and before surgery thiopentone plus nitrous oxide anaesthesia caused changes in blood sugar of about 2 mg/100 ml in either direction. Patients who received morphine-atropine premedication or promethazine-atropine premedication and underwent body surface operations showed rises of up to 25 mg/100 ml though the rises were more marked with the former premedication and during the early part of surgery. This was attributed to respiratory depression after morphine premedication.

Under thiopentone-nitrous oxide-tubocurarine anaesthesia during body surface operations with controlled respiration Dundee and Todd (1958) found a slight but significant rise in blood sugar (up to 7 mg/kg). The rise was less marked in those who received pethidine in addition. It seems, therefore, that although thiopentone anaesthesia does not lead to hyperglycaemia, carbon dioxide accumulation, surgery and lack of analgesia during the surgery, do predispose to a rise in blood sugar.

Initial studies by Podiesch and Angier (1965) and by the author (Clarke and Dundee, 1966a) showed that anaesthesia with propanidid plus nitrous oxide also caused a rise in blood sugar, and that this was larger than in a comparable group given thiopentone. A fuller investigation was therefore carried out to determine whether this was a specific action of the propanidid or was simply related to its shorter duration of action.

METHOD

Investigations were carried out in 120 patients of either sex and in 3 volunteers, 55 of the former receiving thiopentone for induction of anaesthesia and 65 receiving propanidid. Maintenance was with nitrous oxide and oxygen and additional doses of the induction agent and/or tubocurarine as indicated in table I. In those patients who did not receive tubocurarine additional doses of the induction agent were given when small movements of face or limbs indicated lightening of anaesthesia. The technique had been described previously (Clarke and Dundee, 1966b) and with practice smooth operating conditions could be produced, though because of its shorter duration
of action propanidid was less satisfactory than thiopentone. Twenty patients received nitrous oxide-tubocurarine for maintenance (10 induced with each intravenous agent) and a further 10, who received propanidid for induction of anaesthesia, were given additional propanidid at 5-minute intervals to give a deeper level of anaesthesia throughout.

Blood samples were taken in all series before induction of anaesthesia and at 15-minute intervals thereafter from a forearm vein via a Mitchell non-blocking needle. Blood sugar was estimated by the standard auto-analyzer technique. In each series there were approximately equal numbers of patients of each sex receiving the different anaesthetics and age and weight can be seen from table I to be similar in the groups being compared. Premedication in series 1 was atropine 0.6 mg but in series 2 and 3 it varied, with similar numbers in each group being given opiate and non-opiate. No phenothiazine derivatives were given at any time.

The various series of patients in whom blood sugar estimations alone were made are listed in table I, in the order in which they will be discussed. Body surface operations consisted of ligation and stripping of varicose veins, herniorrhaphy and local mastectomy. Induction doses of both drugs were similar in each series, but were appreciably smaller in series 1 than in the others when they approximated more to clinically used doses. All patients given a muscle relaxant were intubated and, after an initial period of manual ventilation, respiration was controlled with a Manley ventilator. In non-relaxant cases (series 1, 3, 4 and 5) gas flows consisted of 6 l./min of nitrous oxide and 2 l./min of oxygen; with relaxant cases the total flow was about 10 l./min, with an inspired oxygen content of 30-40 per cent. Some patients in series 2a received further small doses of induction agent immediately following intubation, this being more often necessary with propanidid than with thiopentone. In series 2b propanidid was given intermittently on an arbitrary basis to a dose approaching that in series 1. In all cases in series 1 and 2 surgery began within 15 minutes of induction of anaesthesia.

In series 3, the minor gynaecological operations lasted between 2 and 10 minutes with an average duration of 4.5 minutes for the thiopentone group and 5.0 minutes for the propanidid group. All the postinduction blood samples were therefore taken with the patients back in bed having regained consciousness. In series 4 three volunteers were given both induction agents on separate occasions.

Glucose tolerance tests (series 5) were also conducted during body surface operations as in the first series. Premedication was atropine 0.6 mg. A sample for blood sugar estimation was again taken immediately before induction with propanidid or thiopentone. A 50 per cent solution of dextrose was then injected rapidly in a dose of 0.33 g/kg and samples were taken at 15-minute intervals after the dextrose for a total of 75 minutes (Conard et al., 1953).

In some cases in series 1 capillary blood was analyzed for PaCO\textsubscript{3} and standard bicarbonate (Andersen, Jorgensen and Astrup, 1960). Blood was obtained from the thumbnail bed and care was taken to see that peripheral circulation was good and that blood was drawn rapidly into the tubes. Observations were made before induction of anaesthesia and at 30- and 60-minute intervals thereafter.

**RESULTS**

The average increases in blood sugar in the series carried out with intermittent intravenous anaesthesia and nitrous oxide during body surface surgery are shown in figure 1. With thiopentone the blood sugar differed significantly from the control level at all time intervals (P<0.001).

![Fig. 1](https://academic.oup.com/bja/article-abstract/40/1/46/245770)

Average increases in blood sugar above the level before induction in twenty patients at 15-minute intervals during body surface surgery (stippled area) (series 1). The open circles represent those who were induced with propanidid and the closed circles those who had thiopentone.
TABLE I
Details of techniques and of patients with average doses of intravenous agents in the various series described. The average initial blood sugar has been given and the standard error where numbers justified this.
(dt = tubocurarine.)

<table>
<thead>
<tr>
<th>Series</th>
<th>Type of operation</th>
<th>Premedication</th>
<th>Maintenance of anaesthesia</th>
<th>No. of patients with each agent</th>
<th>Age (yr)</th>
<th>Wt. (kg)</th>
<th>Initial blood sugar (mg/100 ml)</th>
<th>Induction dose (mg/kg)</th>
<th>Total dose (mg)</th>
<th>Age (yr)</th>
<th>Wt. (kg)</th>
<th>Initial blood sugar (mg/100 ml)</th>
<th>Induction dose (mg/kg)</th>
<th>Total dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Body surface</td>
<td>Atropine</td>
<td>Intermittent i.v. N₂O/O₂</td>
<td>20</td>
<td>45</td>
<td>70</td>
<td>76 ± 3.83</td>
<td>4.2</td>
<td>15.7</td>
<td>1100</td>
<td>48</td>
<td>64</td>
<td>84 ± 1.60</td>
<td>4.2</td>
</tr>
<tr>
<td>2a</td>
<td>Body surface</td>
<td>Opiate/atropine</td>
<td>N₂O/O₂, dtc</td>
<td>10</td>
<td>45</td>
<td>65</td>
<td>87 ± 2.53</td>
<td>5.3</td>
<td>7.1</td>
<td>460</td>
<td>47</td>
<td>63</td>
<td>79 ± 3.25</td>
<td>5.8</td>
</tr>
<tr>
<td>2b</td>
<td>Body surface</td>
<td>Opiate/atropine</td>
<td>Intermittent i.v. N₂O/O₂, dtc</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>51</td>
<td>66</td>
<td>78 ± 4.13</td>
<td>5.8</td>
</tr>
<tr>
<td>3</td>
<td>Minor gynaecological</td>
<td>Opiate/atropine</td>
<td>Intermittent i.v. N₂O/O₂</td>
<td>20</td>
<td>30</td>
<td>58</td>
<td>82 ± 3.11</td>
<td>5.0</td>
<td>5.9</td>
<td>340</td>
<td>34</td>
<td>64</td>
<td>91 ± 2.67</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>3</td>
<td>32</td>
<td>74</td>
<td>88</td>
<td>5.1</td>
<td>—</td>
<td>32</td>
<td>74</td>
<td>84</td>
<td>5.1</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Body surface (glucose tolerance test)</td>
<td>Atropine</td>
<td>Intermittent i.v. N₂O/O₂</td>
<td>5</td>
<td>56</td>
<td>62</td>
<td>72</td>
<td>4.2</td>
<td>15.3</td>
<td>950</td>
<td>40</td>
<td>61</td>
<td>72</td>
<td>4.1</td>
</tr>
</tbody>
</table>
When propanidid was used the increases were significantly greater than with thiopentone at all but the 15-minute sample (30 min, P<0.005; 45 min, P<0.001; 60 min, P<0.025).

To determine whether this increase was related to the dose of anaesthetic another group of body surface operations was carried out using nitrous oxide and relaxant anaesthesia (fig. 2). With the induction dose and only a small incremental dose of thiopentone there was a small rise in blood sugar, significant at 15 minutes (P<0.01), at 45 minutes (P<0.05) and at 60 minutes (P<0.025).

![Figure 2](https://example.com/figure2.png)

**Figure 2**

Average increases in blood sugar in ten patients (series 2). The open circles represent those who had a small total dose of propanidid, the squares those who had a large total dose of propanidid and the closed circles those who had a small dose of thiopentone.

These increases were slightly less than in the non-relaxant series. After a similar regime of propanidid there was a large rise, significantly greater than after thiopentone at all time intervals (P<0.01) and greater than that which occurred in the non-relaxant series. An additional group of patients was given intermittent doses of propanidid to determine whether the dose of anaesthetic had any bearing on the blood sugar response. When propanidid was given intermittently throughout the procedure the increase in blood sugar level, instead of being larger with the larger dose, was smaller. It was still significantly greater than the rise following thiopentone at all but the 15-minute sample (30 min, P<0.01; 45 min, P<0.005; 60 min, P<0.005), and was similar to the rise in the non-relaxant series.

To clarify further the interaction between surgery and the types of anaesthesia the agents were given as an induction dose only, followed by nitrous oxide, to a group of patients having short (under 10 minutes) gynaecological procedures (fig. 3A). The blood sugar rose significantly only after propanidid and this agent caused a significantly greater (P<0.05) degree of hyperglycaemia than thiopentone at 15, 30 and 45 minutes.

![Figure 3A](https://example.com/figure3a.png)

![Figure 3B](https://example.com/figure3b.png)

**Figure 3**

(A) Average increases in blood sugar in twenty patients who had a minor gynaecological operation of short duration (series 3). Conventions as in fig. 1.

(B) Average increases in blood sugar in three volunteers who had a single intravenous dose of propanidid or thiopentone (series 4). Conventions as in fig. 1.

When intravenous anaesthesia was given without surgery to three volunteers (fig. 3B) there was no rise in blood sugar with either agent.

To investigate whether the anaesthetics differed in their effect on glucose metabolism, intravenous glucose tolerance tests were carried out during body surface surgery (series 5). The increases in blood sugar above the pre-anaesthetic level are plotted in figure 4A and clearly there is a different pattern. However, when the mean differences found in the first series are subtracted (fig. 4B) there is little difference between the results with the two agents.

In some of the patients in the first series capillary samples were taken for acid base measurements and table II shows that there were no essential differences between the results with the two drugs. Although there was a small rise in the PCO₂ during thiopentone anaesthesia it was not statistically significant.
Average increases in blood sugar in five patients who had an intravenous glucose tolerance test immediately after induction of anaesthesia (series 5). Results are plotted on a semilogarithmic scale and conventions are as in fig. 1. The left-hand graph (A) shows the increases as obtained but in the right-hand graph (B) the average increases found in series 1 have been subtracted.

**FIG. 4**

**TABLE II**

Average respiratory and metabolic changes during anaesthesia with intermittent propanidid and thiopentone.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>pH</th>
<th>$P_{CO_2}$</th>
<th>Standard bicarbonate (m.equiv/l.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.36</td>
<td>36.6</td>
<td>20.8</td>
</tr>
<tr>
<td>30</td>
<td>7.35</td>
<td>40.1</td>
<td>20.9</td>
</tr>
<tr>
<td>60</td>
<td>7.30</td>
<td>46.4</td>
<td>20.3</td>
</tr>
</tbody>
</table>

**DISCUSSION**

It is evident that under intermittent intravenous anaesthesia with nitrous oxide during body surface surgery, there is a rise in the blood sugar and that this rise is greater using propanidid than thiopentone. On the other hand, this rise is not causally related to the dose of anaesthetic, since in the second series using two dose levels of propanidid the rise is greater with the smaller dose. In fact these results suggest that the rise in blood sugar is related to the psychological or physical stress of surgery even though the sensory impulses do not reach consciousness. This is borne out by the third and fourth series where a similar dose of anaesthetic was given and there was either a transient rise in blood sugar following brief surgery or no rise when there was no surgery. The maximum error in an individual reading was 5 mg/100 ml and in a consecutive series analyzed in one batch about 2 mg/100 ml. Although the resting levels varied widely from patient to patient, the pattern during an operation was remarkably constant, and the increase fairly steady.

The most likely possibility seems to be that during surgery under light narcosis, adrenaline is liberated and that thiopentone even in slightly
lower dosage provides a more continuously deep level of anaesthesia than propanidid. Information about the influence of anaesthetics on the plasma adrenaline level in man has shown that agents tested so far cause no significant increase in the absence of surgical stimulus. This applies to thiopentone, diethyl ether, cyclopropane and halothane (Price et al., 1959), though ether and cyclopropane liberate noradrenaline. However, according to Bearn, Billing and Sherlock (1951) the latter has little effect on metabolism.

While the failure of anaesthesia by itself to liberate adrenaline has been shown, the findings about anaesthesia and hyperglycaemia are less clear. It has been accepted since the beginning of the century (Underhill, 1906) that anaesthesia with diethyl ether leads to a rise in blood sugar and, although surgical trauma and hypercarbia may have played a part in the response (for example, in the cases of Mackay, 1928), it has not been disproved. Chloroform and cyclopropane fall into the same category but it has been shown that halothane anaesthesia is accompanied by no hyperglycaemia during general and neurosurgical anaesthesia (Hunter, 1959). The same is true for methoxyflurane anaesthesia during body surface surgery in children (Black and Rea, 1964). Although there was some controversy formerly, it seems certain that anaesthesia with thiopentone and nitrous oxide does not of itself cause hyperglycaemia in man and even with the additional stimulus of body surface surgery the rise in blood sugar is small (Sessoms et al., 1955; Goldsmith and Holmes, 1957; Dundee and Todd, 1958). Furthermore, the latter two groups have also shown that glucose metabolism is not impaired by thiopentone anaesthesia, and discrepancies between workers may be attributed to species variation and the use of very high dosage in animals.

Race of patient and site of operation also influence the response (Keating, 1958; Keating, Patrick and Annamunthodo, 1959; Cullingford, 1966) but whether the rise is harmful, as these workers have suggested, remains an open question. It would seem worth investigating whether the hyperglycaemic reaction is related to the amount of trauma, and whether it can be prevented, if only to understand more about its mechanism.

ACKNOWLEDGEMENTS

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REFERENCES


AN INTRODUCTION TO RESEARCH TECHNIQUES IN EXPERIMENTAL SURGERY AND ANAESTHESIA

A two-day Course will be held in the Wellcome Surgical Research Laboratories, University of Glasgow, on March 29 and 30, 1968.

The Course will include lectures and demonstrations on animal anaesthesia for experimental surgery, blood-gas measurement and acid-base balance, statistics, application of radioisotope techniques to measurement of blood flow, experimental gastro-enterological and artificial perfusion techniques.

The Course will provide an introduction to basic research techniques for surgeons and anaesthetists.

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