minutes should mitigate against the use of thiopentone as an induction agent.

It is surely true that the degree of depression due to thiopentone is maximal very shortly after intravenous administration of the drug. It must also be remembered that both McKechnie and Converse, and we in this article, are discussing a single injection technique. In both articles it is reaffirmed that with the passage of time the maternal serum thiopentone concentration falls in a uniform manner. Whatever redistribution of thiopentone among the tissues may occur, as time passes the serum concentration gradually falls and the degree of depression gradually diminishes. We have shown, and the few pertinent results recorded by McKechnie and Converse tend to confirm, that, certainly from the three-minute mark onward, the foetal and maternal serum thiopentone concentrations fall synchronously. Surely then it is not too much to suggest that time is of no significance when the single injection thiopentone technique is employed? Assessment of the advisability of administering thiopentone at all must rest on clinical evidence, and we can only claim that a dose of 250 mg has proved apparently harmless in over 200 cases.

ACKNOWLEDGMENTS

Thanks are due to Dr. George Discombe for provision of some of his valuable laboratory space; to Mr. A. Jones, Laboratory Technician, for his help and advice; and to the following volunteers (including three anaesthetists!) for braving the thiopentone injections—N. H. Bruce; E. Cronin; A. V. E. Duthie; M. A. le C. Hills; M. R. MacDonald; E. Bader; F. X. Bencini; A. M. Dawson; J. B. Denny; C. W. Gale; E. M. Rosser; D. G. Wright. Our thanks go also to Mr. J. A. Heady, of the Department of Social Medicine, for the statistical analysis.

REFERENCES


PART II: THE USE OF RELAXANT DRUGS

In collaboration with J. E. GARDINER*

The use of relaxant drugs in obstetric anaesthesia is a practice which appears gradually to have grown without any accompanying attempt to define precisely the indications for their employment. Roughly, there are two objectives: (1) to obtain muscular relaxation at the site of surgical manoeuvre; (2) to facilitate intubation under light anaesthesia. The latter objective is related to the question of vomiting and is discussed in Part III of this article.

With regard to the use of relaxant drugs to permit increased ease of surgical manoeuvre, it would probably be difficult rationally to defend such a practice. For Caesarean section there would appear little need for increased relaxation; for forceps deliveries the advantage of the procedure is open to considerable doubt.

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However, for Caesarean section, and to a lesser extent for forceps delivery, it has become the practice of increasing numbers of anaesthetists to use relaxant drugs.

An obvious danger, early appreciated, is the possibility of placental transmission of the relaxant, leading to a degree of neonatal paralysis. However, following the initial work of Gray (1947), who demonstrated that d-tubocurarine did not appear in the foetal blood, a number of authors confirmed the absence of clinical effects on the child when d-tubocurarine was given to the mother (Whitacre and Fisher, 1948; Corbett and Thomas, 1949; Climie, 1950; Davenport, 1951; Austin and Mering, 1951). None of the latter group of authors substantiated their clinical impressions by analysis of the cord blood.

Apgar and Papper (1952) in their survey of placental transmission, in which the only relaxants discussed were d-tubocurarine and decamethonium, confined themselves to recording that their general impression was that the drugs were not transmitted. Thomas and Gibson (1953) reported similar findings with d-tubocurarine, dimethyl d-tubocurarine, decamethonium and gallamine; again no blood analyses were undertaken. Jewell (1954) in an account of the use of decamethonium for forceps delivery stated that "it is reported that these curare-like drugs do not cross the placenta".

Cohen et al. (1953), in an analysis of nine cases, demonstrated that no d-tubocurarine (Intocostrin) passed through the placenta when doses ranging from 18 to 42 units had been administered to the mother. Somewhat earlier, Pittinger and Morris (1953) had found that d-tubocurarine, when injected in large doses, directly into the uterine artery of pregnant bitches, was transmitted to the placenta to some extent.

The three drugs probably most commonly used in this country to produce relaxation are d-tubocurarine, gallamine, and suxamethonium. The work described below is an investigation into the occurrence of placental transfer of the first two of these drugs.

METHOD

(a) Clinical.

Each patient was given either gallamine triethiodide (80 mg) or d-tubocurarine chloride (15 mg or 20 mg) immediately after induction with thiopentone. No test dose was given. Maternal serum samples "A" and "B" and cord serum sample "C" were obtained as in the thiopentone investigation and a pre-operative maternal sample was also taken.

(b) Biological assay of gallamine and d-tubocurarine.

Gallamine and d-tubocurarine were assayed by a method similar to that of de Jalon (1947) in which the drug antagonizes the acetylcholine contracture of the frog's rectus abdominis. Oxygen and CO₂ were used for aeration, relaxation of the muscle was assisted by electrical stimulation and the timing of operations was automatically performed: with these modifications an increase in sensitivity of 4–5-fold was obtained.

One-half of the longitudinally divided muscle was immersed in a frog Ringer solution (NaCl 6 g/l, KCl 0.15 g/l, CaCl₂·6H₂O 0.3 g/l, NaHCO₃ 0.5 g/l) at room temperature (c. 20°C) and aerated with 95% O₂ + 5% CO₂. The assay cycle
was controlled by an automatic apparatus of the type described by Boura et al. (1954) with automatic addition of the constant dose of acetylcholine (usually 0.3 ml of $10^{-5} M$ solution acetylcholine perchlorate in frog Ringer solution). Relaxation of the muscle after the contracture was aided by a period of electrical stimulation, applied by electrodes at the top and bottom of the bath. Capacitor discharges (1/sec) produced twitches, the rebound of the gimbal lever producing the necessary gentle stretching of the muscle. The cycle of events was thus: (1) manual replacement of bath contents with antagonist solution (4 ml); (2) after 2 minutes, addition of acetylcholine; (3) 90 seconds exposure; (4) two complete washes; (5) 30 seconds electrical stimulation; (6) 90 seconds rest.

Initially, the solutions to be assayed were prepared free of protein by dialysis of the serum against a larger volume of frog Ringer solution, since the frothing, which resulted if serum were added directly to the bath contents, interfered with the assays. Later it was found that the froth could be controlled by the presence of the silicone material M.S. antifoam A, held in the liquid surface throughout the experiment by placing a small amount on the needle introducing the acetylcholine; no deleterious effects on the responses of the muscles were seen. The effects of alternate doses of the serum to be assayed and standards, containing pre-operative serum plus added drug,

![Fig. 4](https://academic.oup.com/bja/article-abstract/28/4/154/243570)

(A) Responses of the frog rectus abdominis preparation to a constant dose of acetylcholine when the antagonist solution contained 0, 0.5, 2.0 μg gallamine triethiodide as indicated below the tracing.
(B) Responses obtained when the antagonist solution contained alternately 0.2 ml of maternal serum (A_M, W_m) or cord serum (A_c, W_c) obtained from two normal deliveries.
(C) Comparison of responses in the presence of 0.2 ml of serum samples from a case receiving gallamine. K_p pre-operative, K_1 first maternal, K_n maternal at delivery, K_c cord sample.
were compared. A final estimate was made proportionately from the two standards most closely straddling the unknown. Normally the amounts of drug contained in the 4 ml of antagonist solution were 0.05–0.30 \( \mu g \) d-tubocurarine chloride, or 0.5–3.0 \( \mu g \) of gallamine triethiodide. Fig. 4A shows the responses obtained when the antagonist solution contained 0.5 or 2.0 \( \mu g \) gallamine triethiodide. The volume of the antagonist solution needed to be carefully measured since the preparation was particularly sensitive to changes in the acetylcholine concentration. Over the mid-portion of the range standards differing by 10 per cent could be used to straddle the unknown, but doses differing by 20 per cent were more common.

The preparation would usually tolerate a maximum of 0.2 ml serum/4 ml solution; Fig. 4B shows the responses recorded in the presence of 0.2 ml of maternal or cord serum from two normal deliveries. Fig. 4C compares the effects of the pre-operative sample with those of the later three samples in a case in which gallamine was used.

RESULTS

Nineteen cases were investigated; 13 received gallamine and 6 d-tubocurarine. None of the infants appeared to be affected by either drug. The mothers were not rendered apnoeic by the dosage of relaxant used, there was no difficulty in their general anaesthetic management. The laboratory results are recorded in table IV.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Maternal weight (kg)</th>
<th>Dose mg/kg</th>
<th>( \mu g/ml ) serum</th>
<th>Time induction to delivery (min)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sample &quot;A&quot;</td>
<td>Sample &quot;B&quot;</td>
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<tr>
<td>Gallamine triethiodide (dose 80 mg)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
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</table>

The case numbers coincide with those given in table I. Sample "A" = maternal plasma 2 minutes after time of injection of relaxant. Sample "B" = maternal plasma at time of delivery. Sample "C" = foetal plasma at time of delivery.
DISCUSSION

In each of the cases which were given gallamine an appreciable concentration of the drug was detected in the cord serum. The amounts found bore no simple relation to the concentration in the maternal serum, neither could the foetal level be related to the dose per unit weight given. There seems almost to be an upper limit to the foetal serum concentration of about 3 \( \mu \text{g/ml} \); this was not exceeded despite the wide variation in dosage (0.90 to 1.55 mg/kg) and in the time elapsing (3–19 minutes) between induction and delivery. The number of cases is too small for this to be definitely established, but it may be that the rate of excretion of the drug by the foetus is sufficient to prevent the foetal serum concentration rising any higher, rather than that there is any limitation on transfer from the mother.

It has been established (Stead, 1955) that infants are more susceptible to the paralysing actions of curare-like drugs than are adults, but whether a serum concentration of 3\( \mu \text{g/ml} \) could be clinically significant is not known; none of the infants in this series appeared to be paralysed. It will be seen, however, from table IV that maternal levels of this order were found after ordinary clinical doses of gallamine, and a more sensitive test of neuromuscular block in the infants might show an effect. There is, therefore, the possibility that the use of gallamine might have to be considered as yet another cause of neonatal depression; in which case, the attempted diagnosis and treatment might well lead to considerable confusion.

On the other hand, the cord serum concentrations of d-tubocurarine were all very low, in four cases insufficient amounts being present to permit normal assay. Again the levels could not be directly related to those in the maternal serum or to the time of delivery. It is possible, therefore, to conjecture that clinically significant amounts of the drug are unlikely to be found circulating in the foetal blood.

SUMMARY

Gallamine triethiodide (13 cases) and d-tubocurarine chloride (6 cases) were given during the course of a series of obstetric operations.

The concentration of the relaxant drug in the serum of two maternal and one cord sample in each case, was determined by a bio-assay method.

With equipotent doses of the two drugs, d-tubocurarine appeared in the foetal serum in traces only, while gallamine occurred in readily detectable and possibly significant amounts.

None of the infants involved appeared clinically to be affected by the procedure.

The rationale of the use of relaxant drugs in obstetric anaesthesia is discussed.

ACKNOWLEDGMENT

Our thanks are due to Professor W. D. M. Paton for his helpful advice and discussion throughout the investigations.

REFERENCES


(To be continued)