It is, however, clear that a high level of serum T.S.H. can be found in cases without ophthalmopathy. If these cases of ophthalmopathy without thyroid disorder are accepted as the same disease, then ophthalmopathy can also exist without a high level of circulating T.S.H.

Thus our assay results could best be explained by assuming that there were two factors involved—one which produces exophthalmos and one which produces thyrotoxicosis. Although both appear to be present in thyrotoxicosis with severe eye signs, they need not necessarily be combined or produce both effects in the one patient. This suggestion has already been made as a result of experimental work in animals, which also implies that the other factor may be derived from the pituitary.

Brown Dobyns (1946) observed that highly purified T.S.H. had relatively little effect in producing exophthalmos in animals. Jefferies (1949) showed that iodination of pituitary extracts inactivated the T.S.H. principle but left some exophthalmos-producing reaction. Dobyns and Steelman (1953) extended the previous observations and were able, by repeated extracting, to produce two substances from the pituitary. In testing these two substances on animals they showed that one contained a T.S.H. free from exophthalmos-producing substance and the other an exophthalmos-producing substance virtually free from T.S.H. These observations, combined with our findings, permit us to support the contentions of De Robertis (1948) and Purves and Griesbach (1949) that T.S.H. alone is not the cause of the development of exophthalmos, and would suggest that the pituitary is also the source of a separate factor, capable of producing exophthalmos.

Summary

A method of assay of T.S.H. has been applied to clinical cases.

So small an amount of T.S.H. circulates in the serum of the normal person that estimation is difficult.

Patients with myxoedema of recent origin and young cretins showed a high level of serum T.S.H., as did most patients with spontaneous myxoedema. The pituitary may ultimately fail to secrete T.S.H. in myxoedema, but this may be reversed by treatment. The high level of T.S.H. in one cretin disappeared with substitution therapy.

Two out of five patients with thyrotoxicosis without severe eye signs showed a raised serum T.S.H., but not to the same level as those with severe eye signs.

Eight patients with thyrotoxicosis with severe eye signs all showed a raised serum T.S.H. level comparable to that of spontaneous myxoedema.

Three patients with severe eye signs without thyrotoxicosis showed levels not differing from those found in normal people.

We conclude that T.S.H. alone is not the cause of exophthalmos, but that some other factor which may also be of pituitary origin is involved.

We thank Dr. Russell Fraser for allowing us access to the patients, most of whom were under his care, and for his constant help and encouragement. Our thanks are also due to Mr. N. W. Please for his help with the statistical analysis, and to Armour Laboratories for their generous provision of the T.S.H. used.

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CONTINUOUS "NISENTIL" AND SUXAMETHONIUM IN ANAESTHESIA

BY

F. M. LANCASTER, M.B., F.F.A.R.C.S., D.A.

Consultant Anaesthetist, Hackney Hospital, London

AND

J. LEVIN, M.B., B.Sc., D.A.

Registrar, Department of Anaesthesia, St. George's Hospital, London, and Hackney Hospital

Continuous suxamethonium drip is proving a beneficial method of obtaining relaxation during anaesthesia for abdominal surgery. Though the method initially proved cumbersome, Green (1953) standardized a useful technique for its use in conjunction with nitrous oxide.

Its chief advantage is that after the drip is stopped full respiratory excursions return within one to five minutes. There is no residual paralysis as occurs when employing the long-acting muscle relaxants. In the light of present-day experience, partial curarization predisposes not only to anoxia but to the danger of undetected carbon dioxide accumulation, and in a very ill patient this may lead to a fatality shortly after leaving the operating theatre (Pask, 1955). The use of neostigmine to antagonize the muscle relaxants introduces undesirable muscarinic side-effects on the myocardium and the bronchial tree. In addition there is difficulty in defining its indication or contraindication in the individual case (Nosworthy, 1953).

The problem of prolonged apnoea which occurs with a single dose of 50 to 100 mg. of suxamethonium is largely eliminated. For by continuous drip administration the anaesthetist is readily able to observe the degree of individual sensitivity and regulate the dosage accordingly.

However, reflex activity, as a result of operative stimuli, may prove difficult to suppress when continuous suxamethonium is supplemented solely by nitrous oxide. The rate of flow of suxamethonium is regulated to produce respiratory arrest to an "end-point." This end-point is respiratory movement just short of diaphragmatic paralysis. It is our experience that the margin of flexibility between the end-point and a degree of paralysis where reflex movement of limbs or spasmodic, jerky contractions of the diaphragm occur is very narrow. Moreover, after discontinuance of the suxamethonium drip the patient regains consciousness too rapidly and may become restless and unmanageable. In some cases psychic trauma may well be a consequence.

Herington and James (1953) employed intermittent doses of pethidine to remedy some of these difficulties.

We in turn have attempted to improve the technique by the admixture of a new analgesic, "nisentil," to the suxamethonium solution.

Nisentil

Nisentil is one of a series of 1-, 4-, 4- substituted piperidines, of which pethidine is a member. Chemically it is D-1, alpha-1,3-dimethyl,4-phenyl,4-propionoxypiperidine hydrochloride. Originally it was known as "Nu 1196." In the United States it has been officially accepted under the name of alphaprodine hydrochloride.

The pharmacological action of nisentil resembles that of pethidine (Gruber *et al.*, 1950). The maximum action of 100 mg. of pethidine is equivalent to between 40 and 60 mg. of nisentil. However, it differs from pethidine in certain important respects. Thus the duration of action of an equivalent dose of nisentil is notably shorter and also the onset of action is more rapid. McCrea and Post (1954) could perform cystoscopy immediately following intravenous administration of nisentil, yet duration of maximum effect was satisfactorily short for this type of procedure. Its main use up to the present has been as an obstetric analgesic. Here it has proved a suitable alternative to pethidine, with the advantage of more rapid onset but shorter duration of action (La Forge, 1951). In anaesthesia it has been used as an analgesic supplement administered by intermittent graded dosage in a similar manner to pethidine or codeine. The work is that of Siker *et al.* (1954). They conclude that it has a minimum cumulative effect, and, compared with pethidine, is therefore more readily controllable.

In view of these properties we believed it to be suitable for prolonged administration by continuous drip with suxamethonium, so that an even blood concentration could be maintained without cumulative effects developing, and in a series of 120 abdominal operations we adopted the following sequence: induction with thiopentone is followed by maintenance with nitrous oxide and a continuous intravenous drip containing 0.01% nisentil and 0.1% suxamethonium in saline.

Technique

Premedication.—Nisentil, 40 mg., and scopolamine, 0.43 mg., were given one hour pre-operatively. If the patient was over 60 years of age, or if his condition was not satisfactory, atropine, 0.65 mg., was substituted for scopolamine. Our original aim in using this particular combination was to obtain a reasonable assessment of any sensitivity to nisentil before administering it under anaesthesia. In no case in our series was there an indication of sensitivity to the drug. At the same time it proved a useful premedicant, especially where morphine or papaveretum was contraindicated.

Use of a Cannula.—When using continuous infusion the point of the intravenous needle may be pushed through the vein wall, and this discredits all the advantages of the anaesthetic method. Splinting of the arm in extension may prevent such an accident. This, however, tends to hinder the surgeon, and in operations requiring the steep Trendelenburg position predisposes to brachial plexus palsy. Therefore the small—1-in. (2.5-cm.)—"Birmingham" and the larger Frankis Evans cannula were inserted routinely in a vein in the forearm. This simple expedient has enabled us to maintain tranquil

intravenous flow with the arm lying by the side of the patient. Where post-operative intravenous fluid is needed it serves a dual purpose.

Induction.—We have observed that thiopentone induction followed shortly thereafter by pethidine intravenously may cause a pronounced fall in blood pressure (as low as 55 mm. Hg systolic). In anticipation of a similar effect with nisentil, the induction dose of thiopentone was kept to a minimum. In this series the average dose amounted to 0.35 g. After venepuncture the thiopentone is injected through the cannula and the previously prepared nisentil-suxamethonium solution is attached to it. The solution is made up by the addition of 50 mg. of nisentil and 500 mg. of suxamethonium to 500 ml. of saline. Since every 50 ml. of solution contains 5 mg. of nisentil and 50 mg. of suxamethonium, a rapid reading of the quantity of each drug administered may be made from the volume markings on the bottle. The bottle is labelled. If the drip is continued post-operatively this serves as a reminder to change the bottle and clear the tubing of the drug solution. The drip is now turned on to flow about 120 drops a minute. Respiration is assisted by inflation with one part oxygen and two parts nitrous oxide. When relaxation is sufficient to allow laryngoscopy the drip is slowed and a cuffed endotracheal tube is passed.

Maintenance.—A flow of 2 litres of nitrous oxide and 1 litre of oxygen a minute is delivered through the closed circuit. The drip rate is adjusted so that minimal diaphragmatic movement is present. Respiration is now carried on by manual compression of the rebreathing-bag. When the peritoneum is closed, carbon dioxide absorption is discontinued and the drip slowed to allow spontaneous respiration to recur. Once the skin wound is being sutured the drip is stopped. Full respiratory volume soon follows and the endotracheal tube is removed.

Drip Control.—An accurately adjustable drip control is essential for this technique. The design illustrated has proved effective. It consists of a frame so ground as to allow for added precision of control. The clamp screw has a fine thread and its wheel control is 2½ in. (6.3 cm.) in diameter. The frame is fitted to a universal "G" clamp, which holds it to the upright of the drip stand. Other uses in the field of continuous drip infusion may suggest themselves with this control.

Results

Troublesome reflex disturbances were notably absent. Combined with the characteristically good muscle relaxation of continuous suxamethonium, maintenance proved uniformly satisfactory.

Of our patients, 56 (47%) awoke or could be roused in the theatre; but the effects of nisentil were such that they were quite comfortable and drowsy on being transferred to the ward. The remainder were asleep on reaching the ward, and, after having recovered their laryngopharyngeal reflexes, were awake within about half an hour. A notable feature was the residual analgesic effect which produced a reduction of restlessness in the immediate post-operative period.

The average time for recovery of full respiration was 3.8 minutes after the drip was stopped. Cumulative effects of nisentil in the form of respiratory depression did not appear in this series.

Apparatus for drip control.

Total Dosage.—The accompanying Table shows the type of operation performed, the average dose-time relationship, and the time taken for full respiratory recovery. The aver-

Summary of Cases

Type of Operation	No. of Cases	Average Time		Average Dose					
		Of Operation (Min.)	To Resume Normal Respiration (Min.)	Thiopentone (g.)	Nisentil		Suxamethonium		
					mg./min.	mg./hr.	mg./min.	mg./hr.	
Partial gastrectomy	22	128	3.6	0.31	0.60	36.1	6.0	361	
Exploratory laparotomy	18	77	4.1	0.34	0.67	40.2	6.7	402	
Ventral, inguinal, and lumbar hernia	16	60	3.2	0.42	0.88	52.9	8.8	529	
Total hysterectomy	11	99	2.5	0.34	0.50	30.2	5.0	302	
Cholecystectomy	11	83	5.6	0.44	0.86	51.8	8.6	518	
Hemicolectomy	8	141	2.8	0.28	0.49	29.3	4.9	293	
Millin's prostatectomy	6	62	5.1	0.25	0.68	40.6	6.8	406	
Ovarian cystectomy	5	64	2.6	0.48	0.60	36.1	6.0	361	
Nephrectomy	3	75	3.5	0.25	0.93	56.0	9.3	560	
Lumbo-dorsal sympathectomy	2	180	5.0	0.40	0.72	43.3	7.2	433	
Oesophagectomy	2	290	5.0	0.30	0.22	13.5	2.2	135	
Adrenalectomy	2	150	3.0	0.25	0.35	20.8	3.5	208	
Abdom. perin. resection rectum	2	115	3.0	0.50	0.70	41.7	7.0	417	
Miscellaneous	12	72	2.5	0.40	0.60	36.0	6.0	360	
Total	120	114	3.8	0.35	0.63	37.8	6.3	378	

age overall dose of suxamethonium was 6.3 mg. a minute, or 378 mg. an hour. This compares favourably with 7.2 mg. a minute or 430 mg. an hour in Green's (1953) original work on continuous suxamethonium. The average dose of nisentil was 0.63 mg. a minute or 37.8 mg. an hour.

Vascular Effects.—The tendency to bleed from the wound was not more than with other relaxant techniques. The pulse rate tended to remain at an even level throughout anaesthesia, though some fluctuation occurred during induction. An initial fall in blood pressure occurred following induction and must be ascribed to the combined effects of thiopentone and nisentil. The fall averaged about 12% of the pre-operative systolic pressure. This was followed by a rapid recovery to a steady level, a little below the initial pre-operative figure. The steady rise in blood pressure reported on by Bourne *et al.* (1952) and de Clive-Lowe *et al.* (1954), using pethidine, was not observed. Calvert and Morgan (1954) thought that suxamethonium has no direct pressor effect. Hypercapnoea as a result of insufficient pulmonary ventilation is the more likely cause of raised blood pressure following prolonged continuous suxamethonium. Efficient assisted respiration and carbon dioxide absorption is thus essential for this technique.

Nisentil with Phenothiazine Derivatives

When first assessing the characteristics of nisentil we combined it in premedication with chlorpromazine and promethazine. Though of some use, it was thought unwise to resort to polypharmacy in premedication. One case, however, proved interesting and is here reported.

A man aged 70 was sent to hospital with signs of acute bowel obstruction. On examination his condition was such as to require immediate laparotomy. He had been gassed in the 1914-18 war and had had chronic bronchitis ever since. For some years attacks of acute asthma complicated his bronchitis. When examined he was in an attack and bronchospasm was marked. Premedication with nisentil, 40 mg., promethazine, 50 mg., and scopolamine, 0.43 mg., was given. An hour later the bronchospasm was a little less severe. Then 50 mg. of chlorpromazine was given by slow drip infusion. As soon as he was well asleep (no thiopentone was used) a nisentil-suxamethonium drip was set up and a cuffed endotracheal tube was passed. At this stage surprisingly little bronchospasm remained and the

lungs were easily inflated. Laparotomy and resection lasted one and a half hours and was uneventful. However, 10 minutes after the drip was stopped bronchospasm, as severe as before, returned. This was relieved by inhalation of isoprenaline and intravenous aminophylline. From the surgical point of view the patient made a good recovery, but his chest condition continued much the same.

Discussion

An objection to the technique described may be that it is not a good principle to deliver an admixture of two drugs simultaneously. But, on the other hand, it is noteworthy that Evans and Gray (1953) employed thiopentone and gallamine by simultaneous infusion with excellent results. It is also becoming increasingly popular to administer "cocktails" of the phenothiazine derivatives with pethidine all at once during induction, and results have proved satisfactory. In each case the agents are longer-acting than either suxamethonium or nisentil.

Though we consider 0.01% concentration of nisentil to be optimal, there is no reason why a smaller concentration (say 0.008%) cannot be profitably used by continuous drip. What is rather more important is the even blood concentration achieved throughout anaesthesia. In this respect Slaughter (1950) observed that after a single dose of 20 mg. of nisentil, doubling that dose did not appreciably increase analgesic activity.

In view of the useful bronchodilator effect produced by the combination set out in the case report, it is suggested as an anaesthetic procedure for trial when the patient is in an attack of asthma or as a prophylactic measure to avoid bronchospasm during anaesthesia.

Summary

The properties of the new short-acting analgesic nisentil are discussed. Nisentil 0.01% and suxamethonium 0.1% in saline were used by continuous drip to supplement nitrous oxide anaesthesia.

In 120 abdominal surgical cases delivery of analgesic supplement in this manner gave satisfactorily uniform control.

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King Edward's Hospital Fund for London continues in its 58th report, covering the year 1954, its story of voluntary effort and initiative in hospital service. It has made many grants to hospitals for projects outside State provision—for the promotion of comfort in the wards, recreation halls and canteen facilities for staff, occupational therapy huts, social centres, and the like. It has also encouraged improvements in the care of elderly patients and has assisted children's convalescent homes. It has established training centres for hospital administrators, for ward sisters, for hospital cooks and caterers, and for matrons. In its division of nursing it has sought through a recruitment service to guide candidates to suitable courses of training. Its administrative staff college has seen a steady development. Its hospital catering advisory service undertook during the year five major surveys. But perhaps of all its undertakings the emergency bed service, which has recently registered its 500,000th application, appeals most to the busy general practitioner.