Notwithstanding these remarks, in the absence of any other data, the results obtained in this trial cast very grave doubts upon the claims made for the preparation used.

Summary

A small controlled trial has been carried out with six subjects and six controls of the effect of "geriopil H3" on the mental ability, as measured by a number of psychological tests, of patients with senile or arteriosclerotic dementia. The trial has failed to prove that geriopil is of any value in this respect.

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RESPIRATORY PARALYSIS AFTER A LARGE DOSE OF STREPTOMYCIN

REPORT OF A CASE

BY

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A number of cases have been reported in which intraperitoneal administration of neomycin in large dosage has been followed by the development of post-operative respiratory insufficiency or apnoea (Pridgen, 1956; Poth, 1957; Middleton *et al.*, 1957; Engel and Denson, 1957; Ferrara and Phillips, 1957). Streptomycin has been shown to be capable of blocking neuromuscular conduction in experimental animals (Brazil and Corrado, 1957; Bezzi and Gessa, 1959), and in human intercostal nerve-muscle preparations (Sabawala and Dillon, 1959). Loder and Walker (1959) have reported three cases of muscular weakness and visual difficulty, resembling a myasthenic state, in patients receiving standard intramuscular doses of streptomycin. The symptoms were relieved by neostigmine and by withdrawing the streptomycin.

Streptomycin is not infrequently instilled into the peritoneal or pleural cavity at the end of some surgical procedures, and Bush (1961) has described the occurrence of prolonged post-operative apnoea in a child aged 6 months, which he attributes to neuromuscular blockade by the combination of D-tubocurarine and a large dose of streptomycin (1 g. intraperitoneally). I feel that a similar case occurring in an adult is worth reporting.

Case Report

The patient, a fit man aged 53, had a stricture of the lower end of his oesophagus. An oesophageal hiatus hernia had been repaired nine weeks previously, when he was noted to be somewhat resistant to anaesthetic drugs. His weight

was 12 st. (76.2 kg.), haemoglobin 13.8 g./100 ml., and blood pressure 135/80 mm. Hg; he was classed as a good risk for anaesthesia and surgery. The proposed operation was an ileocaecal transplant and anastomosis for relief of the oesophageal stricture.

Premedication with papaveretum 20 mg. and scopolamine 0.4 mg. was given at 8 a.m. At 9 a.m. thiopentone 0.4 g. and then suxamethonium 50 mg. were given intravenously, the lungs were inflated with oxygen, and 2 ml. of 5% cocaine solution was instilled into the trachea, followed by intubation with a No. 10 cuffed Magill tube.

Operative Course

When the ileocaecal transplant had been mobilized and anastomosis with the oesophagus started, its blood supply was found to be inadequate. The ileocaecal transplant was therefore resected and replaced by jejunum, the whole procedure lasting seven hours. The patient was resistant to the drugs used, and a total of 87 mg. of D-tubocurarine and 170 mg. of pethidine, and a further 0.2 g. of thiopentone, were required to control "bucking" and straining. He was ventilated throughout with nitrous oxide and oxygen, by the Blease pulmoflator or by hand through a Waters canister. The blood-pressure was steady at about 110 mm. Hg systolic except for a short period when it fell to 90 mm. Hg, when 9 mg. of methylamphetamine was given. The blood loss, measured by weighing the swabs and adding to the loss via suction, was 1,030 ml., and 1,500 ml. of whole blood was replaced together with 1 g. of calcium gluconate. Before the wound was closed a total of 10 g. of streptomycin powder was administered, 5 g. being placed in the peritoneal and 5 g. in the pleural cavity. Spontaneous respiratory movements began during closure, after which atropine 1.2 mg. and then neostigmine 2.5 mg. were given intravenously. The patient left the theatre at 4 p.m., when his general condition was satisfactory, his blood-pressure being 110 mm. Hg systolic, and respiratory function appeared adequate.

On the way back to the ward, respiratory movements diminished greatly over a period of two to three minutes, becoming very shallow. The patient was rapidly returned to the theatre, reintubated, and ventilated with oxygen. The state of his circulation was quite satisfactory at this time, blood-pressure being unaltered. Atropine 0.6 mg. intravenously, followed by two doses of 1.25 mg. of neostigmine, resulted in a marked improvement in spontaneous ventilation, which lasted for less than a minute on each occasion. 2 ml. of nikethamide had no effect. At this stage the blood-pressure fell abruptly and became unrecordable. Intravenous methylamphetamine 30 mg. brought the pressure up to 70 mm. Hg. Additional blood was transfused and hydrocortisone 100 mg. given intravenously. Soon after this the blood-pressure was 120 mm. Hg and his cardiovascular state caused no further anxiety.

Respiratory movements were still very feeble, and the patient was therefore connected to a Barnet ventilator and inflated with oxygen. After a few minutes, assistance by means of the patient-triggering device was sufficient. This was necessary for another hour, during which he became responsive to commands to move his eyelids and head. Towards the end of this time he was able to open his eyes and wrinkle his forehead. At this stage the ventilator was disconnected and he breathed air through the endotracheal tube with no cyanosis, although there was still some tracheal tug and mild ptosis with a "myasthenic facies." Forty minutes later the endotracheal tube was removed. Ventilation was adequate, with only slight tracheal tug and facial weakness. The patient now complained of pain from the incision, and papaveretum 10 mg. was given subcutaneously, with some relief of pain but no adverse respiratory effect. He was finally returned to the ward in a satisfactory condition at 6.30 p.m., and made an uneventful recovery, having no recollection of the events in the immediate post-operative period. However, for some days afterwards he was subject to undefined frightening dreams, and said that he felt a little afraid of falling asleep in case he did not wake up.

Discussion

Initial studies by Molitor *et al.* (1946) on the acute toxicity of streptomycin in animals showed that respiratory depression was the main acute effect of a large overdose and the cause of death in fatal dosage. They showed that artificial ventilation enabled animals to survive an otherwise fatal dose, and that in much larger doses still there was a severe fall in blood-pressure.

Brazil and Corrado (1957) demonstrated a neuromuscular blocking effect of streptomycin, suggesting that this was the cause of the respiratory depression from toxic doses. They found that the block resembled that due to magnesium ions rather than that due to D-tubocurarine, in that post-tetanic facilitation was initially maximal and the block was more fully reversed by calcium ions than by neostigmine, though both were effective.

Bezzi and Gessa (1959) noted an increased susceptibility to D-tubocurarine of patients receiving large doses of some antibiotics, and showed that streptomycin could potentiate the effect of D-tubocurarine in rabbits.

Sabawala and Dillon (1959) demonstrated the neuromuscular blocking action of streptomycin in preparations of human intercostal muscle. They found that it was antagonized by neostigmine, and was about three-tenths as potent as neomycin.

Neuromuscular blockade by streptomycin in the absence of other factors seems to be rare (Loder and Walker, 1959). Bush (1961) suggests that in his case the combination of a very large dose of streptomycin with the use of a non-depolarizing relaxant was responsible for a prolonged neuromuscular block. In the present case the combination of a very large dose of both D-tubocurarine (87 mg.) and streptomycin (10 g.) could have caused the respiratory insufficiency. It is realized that recurarization may have occurred under these conditions without the aid of streptomycin, although the fact that spontaneous respiration was present before neostigmine was administered would suggest that this was unlikely. In view of the work of Brazil and Corrado, perhaps further intravenous doses of calcium gluconate may have been indicated.

In the reports of respiratory depression after large doses (5 to 10 g.) of intraperitoneal neomycin, patients who had been breathing adequately when closure of the abdomen was started became apnoeic some 15 to 20 minutes later. In this case it was some 30 to 40 minutes after the streptomycin was instilled that the effect was noted. The later fall in blood-pressure could have been a toxic effect of a very large dose of streptomycin (Molitor *et al.*, 1946), although the changes in ventilation and drugs used at the time are also possible factors.

Introduction of a large dose of streptomycin into the pleural or peritoneal cavity carries the theoretical risk of increasing neuromuscular block when muscle relaxants are being used. Although the part played by streptomycin cannot be proved in the present case, it is felt that the circumstances strongly suggest a practical as well as a theoretical hazard.

Summary

A case is described of post-operative respiratory insufficiency in which a very large dose of streptomycin had been introduced into the body cavities after a large dose of D-tubocurarine given during the course of an operation lasting seven hours. The pharmacological

evidence for a neuromuscular blocking action of streptomycin is reviewed and it is suggested this action was responsible for the complication described.

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Medical Memoranda

Prolonged Neuromuscular Block Due to Intraperitoneal Streptomycin

Neuromuscular block of a non-depolarizing type has been produced in animals by certain antibiotics. Neomycin (Pittinger and Long, 1958), streptomycin (Vital Brazil and Corrado, 1957), and polymyxin B (Sabawala and Dillon, 1959) have been shown to have a blocking action on the muscle end-plate. A similar effect has been described in humans after the intraperitoneal instillation of neomycin (Pittinger and Long, 1958) and the parenteral injection of streptomycin (Loder and Walker, 1959).

In the following case a persistent neuromuscular block was believed to have been due to intraperitoneal streptomycin sulphate.

CASE HISTORY

A male infant aged 6 months and weighing 13 lb. (5.9 kg.) was presented for rectosigmoidectomy for Hirschsprung's disease. Since a transverse colostomy at the age of 2 weeks the baby had thrived.

Atropine sulphate, 0.3 mg., was given at 9.30 a.m., and anaesthesia was induced at 10.30 a.m. with thiopentone sodium, 20 mg., followed by D-tubocurarine chloride, 4 mg., given into an intravenous infusion. Intubation was performed with a size 0 Magill orotracheal tube, and anaesthesia was maintained with N₂O and O₂, 4 and 3 litres a minute respectively, with controlled ventilation given by Rees's (1959) modification of Ayre's T-piece. The operative procedure consisted of a hemicolectomy and lasted four hours, during which another 4 mg. of D-tubocurarine chloride, given in divided doses, was required to secure adequate control of respiration; the last 1 mg. was given one and a half hours before the end of the operation. Blood loss was 66 ml., and 110 ml. of blood was given during the surgical procedure. Spontaneous respiration was resumed 45 minutes before the end of the operation, but with the aid of continued hyperventilation relaxation was deemed to be adequate to permit closure of the abdomen.

Streptomycin sulphate was instilled into the peritoneal cavity; inadvertently 1 g. was administered. It was noticed that the relaxation became more complete and attempts at spontaneous respiration ceased. The possible significance of this was not appreciated at the time. Atropine sulphate, 0.12 mg., was given intravenously at 2.30 p.m., and with the resumption of spontaneous respiration 0.5 mg. of