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Pancuronium bromide—A new non-depolarizing muscle relaxant

Preliminary report on its use in fifty patients

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MUSCLE relaxants are used to provide better operating conditions for the surgeon, by lessening the depth of anesthesia required for a specific degree of muscle relaxation.

According to Bennett,[1] Bernard was the first physician to demonstrate the ability of curare to block neuromuscular transmission in 1850. The drug was not used clinically until 100 years later, when it was employed to prevent traumatic complications of electroconvulsive therapy. In 1942, curare (intercostrin) was used during general anesthesia to provide muscular relaxation.[2] The next year, d-tubocurarine methyliodide was introduced and has remained the most widely used non-depolarizing muscle relaxant[2] despite much research work directed toward developing new and better agents.

Our report concerns the use of a new drug, pancuronium bromide,† as a muscle relaxant in 50 patients who each underwent one of 20 different operative procedures. We believe that pancuronium has these advantages over other non-depolarizing muscle relaxants currently in use: rapid onset of action; no release of histamine; and only slight ganglionic blocking action.

Pharmacologic features

One way of developing new therapeutic agents is to incorporate a biologically active group into a substance occurring naturally in the body. This method is the basis of the synthesis of the new muscle relaxant, pancuronium bromide.[3] Quaternary ammonium and ester groups were incorporated into a steroid nucleus (*Fig. 1*) to produce the new drug, which was found to be a potent neuromuscular blocking agent.

The neuromuscular block produced by this drug was studied[3] in anesthetized cats and conscious mice and rabbits, and proved to be of a non-depolarizing type as characterized by: (1) no fasciculation, (2) "fade" of

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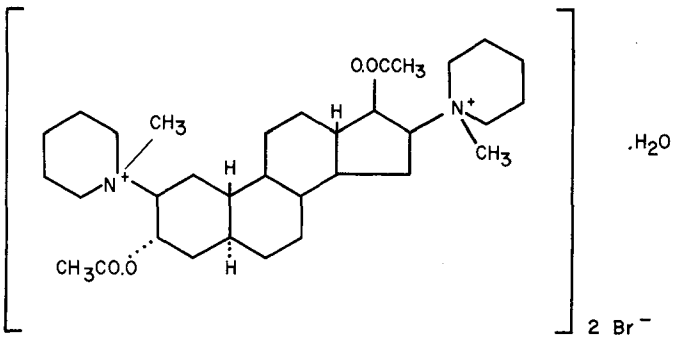

Fig. 1. Chemical structure of pancuronium bromide: 2β,16β-dipiperidine-5α-androstane-3α,17β-diol diacetate dimethobromide.

tetanic stimulation, (3) posttetanic facilitation, (4) reversal of action by neostigmine.

Potency. The effect of pancuronium bromide was compared to that of d-tubocurare in various species of animal—rabbit, cat and dog. In man the study was carried out by Baird and Reid[4] who used ulnar nerve-hypothenar muscle stimulation. Pancuronium was found to be about five times as potent as curare, 25 times more potent than gallamine triethiodide and 15 times more effective than suxamethonium chloride. The dose, advised on the basis of weight, was from 0.05 to 0.1 mg per kilogram of body weight.

Toxicity. Pancuronium causes a specific effect on neuromuscular action and, when ventilation was supported, large doses produced no ill effect. In animals 25,000 times the neuromuscular blocking dose was administered without mortality.[3]

Duration and reversal of action. A dose of 6 mg will give an average effective period of 45 minutes. The action of pancuronium was found to be enhanced by ether, halothane, cyclopropane,[5] and methoxyflurane, and also by the antibiotics neomycin and streptomycin. Hypothermia shortens the duration and diminishes the potency of pancuronium.[2]

Reversal of drug effect is readily achieved by cholinesterase inhibitors, thus neostigmine reverses the paralysis without difficulty, and apparently does so more rapidly and more completely than with tubocurarine or gallamine.

Metabolism and excretion. The fate of pancuronium is still being studied, but from preliminary results it has been shown to disappear from the circulation in two phases: a rapid phase of 5 to 10 minutes, followed by a slower phase where circulating levels fall more gradually. Results suggest that the drug is not chemically altered in the body. The highest levels of radioactivity, 30 minutes after injection of isotope-labeled pancuronium, were found in the liver, kidney, and urine. Although pancuronium has been isolated in an unchanged form in the urine, no increase in the duration of muscle relaxation was noted in nephrectomized cats.[6]

Table 1.—Age and sex distribution of 50 patients who received pancuronium for muscle relaxation

Age range, years	Patients, number		
	Females	Males	Total
10 to 20	2	2	4
21 to 30	2	1	3
31 to 40	4	1	5
41 to 50	4	3	7
51 to 60	3	11	14
61 to 70	3	7	10
71 to 80	2	5	7
Total			50

No positive relation is known between the steroid nucleus of the drug and naturally occurring body steroids.

Radioactivity was detected in fetuses after administering isotope-labeled pancuronium to pregnant animals.

Material and methods

The drug was used in 50 patients, 20 females and 30 males, whose ages ranged from 13 to 78 years (*Table 1*). The 50 patients underwent 20 different surgical procedures ranging from simple abdominal to major vascular operations (*Table 2*).

The following anesthetic technics were employed. (1) Induction with thiopentone sodium followed immediately by administration of pancuronium. Manual ventilation was then performed for two or three minutes, after which the patient was intubated. Anesthesia was maintained with: $N_2O + O_2 + 0.3\% - 0.5\%$ methoxyflurane (25 patients); $N_2O + O_2 + 0.5\%$ halothane (13 patients); $N_2O + O_2 +$ intermittent doses of 0.5 mg oxymorphone (6 patients). (2) Administration of droperidol-fentanyl,* followed by pancuronium, ventilation and intubation, anesthesia being maintained with N_2O, O_2 and supplemental fentanyl (6 patients).

The initial dose of pancuronium was 0.1 mg per kilogram of body weight. This provided satisfactory conditions for intubation within two to three minutes of injection. The larynx was immobile and no cough resulted after insertion of the endotracheal tube. The duration of action of the initial dose varied according to the anesthetic technic; for example, with methoxyflurane the effect was more prolonged than with N_2O, O_2 or with droperidol-fentanyl. On the average, a 6-mg initial dose had a duration of action of from 45 to 60 minutes, at which stage muscle tone began to return. Incremental

* *Innovar.*

Table 2.—Number and types of operative procedures in which pancuronium was used

No.	Type of operation	Number of patients
1	Resection of aortic aneurysm	11
2	Colon resection	4
3	Submucous resection and trimming of turbinates	4
4	Thoracotomy (lobectomy or pneumonectomy)	4
5	Exploratory laparotomy with biopsy	3
6	Femoral bypass graft	3
7	Sympathectomy (thoracic, lumbar)	3
8	Abdominoperineal proctosigmoidectomy	2
9	Bilateral adrenalectomy	2
10	Cholecystectomy with cholangiography	2
11	Gastrojejunostomy	2
12	Thyroidectomy	2
13	Aortic renal endarterectomy	1
14	Carotid endarterectomy	1
15	Donor nephrectomy	1
16	Innominate artery bypass graft	1
17	Parathyroidectomy	1
18	Mitral valve replacement (extracorporeal circulation)	1
19	Pheochromocytoma	1
20	Pulmonary embolectomy	1

Table 3.—Doses of neostigmine required to reverse action of pancuronium*

Neostigmine dose, mg	2	2.5	3.0	3.5	4.5	5
Patients, number	1	16	4	19	2	1

* In 8 patients action of pancuronium was not reversed (see text).

doses of 2 mg were given to maintain relaxation, as judged clinically by changes in lung compliance, and comments by the surgeons relevant to muscle tightening. The longest procedure lasted seven and one-half hours, the shortest, one hour. The maximum total dose of pancuronium in this series of patients was 15 mg. No difficulty was encountered in reversing the drug effect in any of the patients. Moderate hyperventilation was employed as an adjunct to the other details in anesthetic management, arterial pCO_2 levels being maintained between 30 and 35 mm of Hg.

Results

Relaxation obtained by the use of pancuronium was judged to be excellent, by assessing total lung compliance, tone of abdominal musculature (surgeons' comments), and nerve stimulation performed with a Block Aid Monitor.

Reversal of action. The action of pancuronium was easily reversed by the use of a neostigmine-atropine combination. Less than half of the patients required 3.5 mg of the neostigmine to have the effect of the drug reversed completely, as evidenced by: the patient's ability to lift head, manual grip, tidal volume measured by anemometer, inspiratory pressure gauge, phonation.

In patients where it was elected to employ prolonged controlled ventilation, no anticholinesterase drugs were used. Those patients were extubated in from one to eight hours postoperatively, and no difficulties were encountered. When the action of pancuronium was reversed by neostigmine, there were no instances of recurarization. In *Table 3* are listed the number of patients and doses of neostigmine they needed to reverse the action of pancuronium.

Adverse effects. The only adverse effect that could have been caused by pancuronium was tachycardia, which occurred in two patients. In those patients the tachycardia developed during the course of the operation, and other causative factors could not be excluded. Transitory atrial fibrillation developed in one patient during surgical manipulations in the region of the lung root.

Summary and conclusions

A new non-depolarizing muscle relaxant, pancuronium bromide, has been used in preliminary clinical trial in 50 patients. It offered several distinct advantages over drugs already available, while causing no apparent undesirable effects. The advantages include more rapid onset of action; no release of histamine; and little disturbance in blood pressure, because of a weak ganglionic-blocking action. Further evaluation of pancuronium bromide will be conducted on a double-blind basis.

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