PANCURONIUM AND THE NEONATE

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SUMMARY

Pancuronium bromide was used safely as the muscle relaxant for neonatal anaesthesia. No untoward effects were seen and the neuromuscular block was successfully reversed in all patients. The potency ratio of pancuronium as compared with tubocurarine ranged from 9:1 at birth to 6:1 at one month of age.

The newborn is increasingly subjected to major surgical procedures, and the anaesthetic techniques used commonly involve muscle relaxants. This study was performed to determine if pancuronium bromide is suitable for use in anaesthesia at this age, and to attempt to establish an index of dose and potency for this drug.

METHOD

All the surgical procedures were upon the abdomen. Thus muscle relaxation and apnoea could be better judged and the patients' general condition was less complicated than in those with cardiac, thoracic, or neurosurgical conditions. Twenty-five patients were studied. All were under 28 days of age at the time of the procedure. Pancuronium was given in a strength of 100 μg/ml. All neonates were premedicated with atropine 0.1 mg i.m., 1 hour before operation.

On the operating table the patient was placed on a warm water mattress, maintained at a temperature of 40°C. After ascertaining that the stomach had been decompressed and that secretions, if any, had been removed from the pharynx, an orotracheal tube was inserted while the infant was awake. A 50:50 mixture of nitrous oxide in oxygen was then given using the Rees variation of the Ayre's T-tube, with a total flow rate of 4 litre/min. The initial dose of pancuronium, 50 or 100 μg, depending upon whether the infant weighed less or more than 2.27 kg, was injected intravenously. The time of onset, and the effect of this dose, were assessed. Full control of ventilation and adequate relaxation were used as the end-points. No attempt was made to assist or control ventilation until apnoea was observed. An Argyle "Medicut" cannula, 18 gauge, was placed percutaneously in the arm or the foot, and 5% dextrose in lactated Ringer's solution was infused at a rate of 8 ml/kg/hr.

The duration of action of pancuronium was assessed as the interval from apnoea until there was a need for an incremental dose or until the block could be antagonized. Using a potency ratio, derived from the literature, of 5:1 for pancuronium compared with tubocurarine, the initial dose was 50 or 100 μg, according to the weight. It was soon noticed, however, that almost all the smaller and the younger infants became apnoeic with this dose and required no further doses. The initial dose was then reduced to 25 or 50 μg respectively if the infant was less than 7 days old. In all the babies the block was reversed with a mixture of atropine 0.018 mg/kg and neostigmine 0.08 mg/kg given i.v.

RESULTS AND DISCUSSION

The amounts of pancuronium necessary to produce the desired effects, in each patient, can be seen in figure 1. Table I lists the dose necessary for each newborn to establish the proper conditions. Figure 2 is a reproduction of the data of Bush and Stead (1962) for tubocurarine. Figure 3 shows the regression lines from figures 1 and 2 and it can be seen that the two slopes are significantly different. If potency is determined from these lines, the potency ratio of pancuronium is approximately 9 times that of tubocurarine at one day of age, and this ratio decreases progressively to a ratio of 6:1 at 28 days of age. At 7 days of age, the ratio is 8:1, and at 14 days of age, 7:1.

There is no doubt that the neonate is sensitive to pancuronium. The dose required for relaxation and apnoea at one day of age is 40 μg/kg, a dose which in the presence of 50% nitrous oxide in
the sensitivity to pancuronium becomes less; relaxation and apnoea were obtained only after 92 µg/kg at 28 days of age.

A nerve stimulator was not used to test the response of these neonates. If the effect of a muscle relaxant is to be tested in the presence of minimal anaesthesia, two factors need to be considered. First, the effect of supramaximal stimulation upon the neonate and his response (Churchill-Davidson and Wise, 1963). Secondly, the observation that there needs to be an occupancy ratio of 25–50% for the peripheral muscles and 50–75% for the diaphragm for any effect of a non-depolarizing block to be appreciated (Waud and Waud, 1972a,b). Since it was the clinical effects that were being observed, and as the neonate reacts to nerve stimulation in such a way that recordings are not practical, apnoea was used as the end-point.

In comparing the drug requirements with respect to age and weight, the potency of pancuronium is 6–9 times that of tubocurarine. In none of our patients was there evidence that the block failed to reverse adequately. There was no evidence of abnormal cardiovascular responses although these were not studied specifically. The time from injection of pancuronium to onset of paralysis was 30 sec to 1 min depending upon the intensity of the effect. The duration of the block varied between 50 and 90 min, from full apnoea until reversal could be accomplished or an increment was necessary. Stead (1955) investigated the action of tubocurarine in the newborn in a study of neonates less than 48 hours old undergoing surgical proce-
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dures. He used the abolition of respiration as an endpoint. His conclusion was that the newborn was exquisitely sensitive to tubocurarine and he likened the newborn neuromuscular junction to that in myasthenia gravis. Bush and Stead (1962), reporting on 215 babies in the first month of life, repeated this finding (fig. 2).

However, Walts and Dillon (1969), reporting on another study with the newborn, doubted that this was so. If body weight was used, their results agreed with the earlier study, but they suggested that using another parameter, such as surface area, the "myasthenia response" was not present. They studied 15 patients of whom only four were truly newborn, and four were over the age of 28 days; five patients had pyloric stenosis, of whom three had a metabolic acidosis. Churchill-Davidson and Wise (1964) also reported that the neonatal neuromuscular response was not different from that of the adult. But their series contained only three patients aged 1, 2, and 3 weeks respectively. Yamamoto, Baba and Shiratsuchi (1972) reported on the effects of pancuronium in children. They noted that there were four children under one month of age without commenting upon any specific effects. The ages of these four were not given. They used a dose of 80 μg/kg and obtained a duration of action of 42 min approximately. The results of the present study agree with those of Bush and Stead, that the newborn is sensitive to non-depolarizing muscle relaxants, that this sensitivity diminishes with age to the extent that, at one month of age, the motor endplate has an almost normal response. This study shows that pancuronium is similar in its effects to tubocurarine. The potency ratio of pancuronium to tubocurarine is 6:1 to 9:1, at this dose level and for this age group. This potency ratio has been suggested with adults receiving large doses, and Lund and Stovner (1970) have shown that the potency varies with the dose from 5:1 to 7.5:1.

It is now our practice to administer pancuronium to the newborn in the following doses:
- 0–1 week: 30 μg/kg
- 1–2 weeks: 60 μg/kg
- 2–4 weeks: 90 μg/kg

This dose is reduced in prematurity, acidosis, hypothermia, or in other conditions in which the sensitivity to pancuronium can reasonably be expected to be increased, including antibiotics.

The clinical end-point, control of respiration and muscle relaxation, is achieved by giving additional amounts of pancuronium, 1/4 to 1/2 of this initial dose. Throughout the procedure, if incremental doses are required, 1/5 to 1/6 of the dose required to achieve the end-point is given. The maintenance anaesthetic is 50% nitrous oxide in oxygen with controlled respiration. The duration that can be expected at this dose range is 75 ± 20 min. Predictability of this effect has been reported by Deschene, Desrosiers and Bedard (1972) in adults. At the end of the procedure, the residual effects of pancuronium are reversed with a mixture of atropine, 0.018 mg/kg, and neostigmine, 0.08 mg/kg, given intravenously in all cases.

The cause of the sensitivity of the neonate to non-depolarizing drugs is not known. It may be that a different parameter is required, such as extracellular fluid volume, or body surface area. It may also be the result of differences in protein binding, or an alteration in the response of the motor endplate, or prejunctional receptors. However, for practical purposes, body weight remains the easiest measurement to make and apply in the operating room. In the assessment of the newborn, conceptual age (the age from conception), would appear to be more important than actual age and will allow for premature/postmature differences in response. Of course the use of potent anaesthetic drugs, such as halothane, ethrane and ether, alters the amounts of non-depolarizing relaxants that should be given.

Some neonates were eliminated from the series where it was apparent that antibiotics had been administered for more than 5 days and increased sensitivity was observed. Kanamycin and gentamycin were the antibiotics which were associated with the most notable effects.

CONCLUSION

Pancuronium is effective as a muscle relaxant for the newborn and it appears that the newborn response is "myasthenic" in type as it is with tubocurarine. This study would appear to indicate that the potency of pancuronium is at least 6–9 times that of tubocurarine for the doses studied.

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REFERENCES


LE PANCURONIUM CHEZ LES NOUVEAUX-NES

RESUME

Le bromure de pancuronium a été employé de manière sûre comme médicament relâchant pour l’anesthésie néonatale. Aucun effet fâcheux n’a été remarqué et l’anesthésie s’est trouvée effectivement inversée dans tous les patients. Le rapport d’efficacité du pancuronium par rapport à la d-tubocurarine allait de 9 à 1 à la naissance à 6 à 1 à l’âge d’un mois.

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PANCURONIUM BEI NEUGEBORENEN

ZUSAMMENFASSUNG


PANCURONIUM EN RECIENT NA CIDOS

SUMARIO

Se empleó satisfactoriamente bromuro de pancuronium como relajante para anestesia neonatal. No se observaron efectos desfavorables y la anestesia tuvo un efecto de reversión eficaz en todos los pacientes. La relación de potencia del pancuronium comparado con d-tubocurarine varió entre 9:1 al nacimiento y 6:1 a la edad de un mes.