SUXAMETHONIUM-NEOSTIGMINE INTERACTION IN PATIENTS WITH NORMAL OR ATYPICAL CHOLINESTERASE

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SUMMARY

The effect of neostigmine 0.05 mg/kg on the neuromuscular block produced by suxamethonium was investigated in 10 normal patients and in five patients with atypical plasma cholinesterase activity, by recording the twitch response to ulnar nerve stimulation. In the normal patients, neostigmine potentiated the block produced by suxamethonium whether it was of the depolarizing or desensitizing type. On the other hand, in patients with atypical plasma cholinesterase activity, neostigmine potentiated the depolarizing phase of suxamethonium block, while antagonizing the desensitizing phase. The degree of antagonism was not related to the magnitude of neuromuscular block, but was proportional to the degree of desensitization at the time of antagonism.

Baraka (1975a) has shown that the interaction of suxamethonium with hexafluorenium, a selective plasma cholinesterase inhibitor, differs in normal patients from that in patients with atypical plasma cholinesterase activity. In normal patients, hexafluorenium results in marked potentiation of suxamethonium block, while in patients with the atypical enzyme there is no potentiation or even a diminution of the response.

Neostigmine is an inhibitor of both plasma- and acetylcholinesterases (Irwin and Smith, 1960). Therefore, the suxamethonium-neostigmine interaction might differ also in patients with normal plasma cholinesterase activity from that in patients with the atypical enzyme.

This report compares the suxamethonium-neostigmine interaction in patients with normal and atypical esterase.

METHODS

Fifteen patients undergoing elective surgical procedures were investigated. Ten had normal plasma cholinesterase activity while the other five were atypical cholinesterase homozygotes.

The relative plasma cholinesterase activity and the dibucaine number were measured in the patients investigated. The cholinesterase activity was measured by the method of Michel (1949), while the dibucaine number was estimated by the method described by Kalow and Genest (1957). In the normal patients, the relative cholinesterase activity was 80–110% of normal while the dibucaine number ranged from 74 to 81.

In the atypical homozygotes, the relative cholinesterase activity was 13–19% of normal, while the dibucaine number ranged from 22 to 30.

Anaesthesia was maintained with nitrous oxide in oxygen (2 : 1) and halothane 0.5%. The ulnar nerve was stimulated with a Block-Aid monitor at 0.25 Hz. The resultant thumb adduction was monitored by a Grass force displacement transducer (FT 03) connected to a Grass polygraph. After a steady twitch response was obtained, the following observations were made.

Normal esterase homozygotes. In five normal adult patients, a bolus of suxamethonium 0.1 mg/kg was injected i.v. and the neuromuscular block was recorded. After complete recovery of neuromuscular transmission, a mixture of neostigmine 0.05 mg/kg and atropine 0.02 mg/kg was injected and followed 1 min later by the same dose of suxamethonium (0.1 mg/kg). The resultant block was compared with the control response.

In a second group of five normal adult patients, suxamethonium 0.1% was infused continuously to produce a twitch response about 25% of the control. The type of block was determined by the response to tetanic stimulation. When desensitization block was established, a mixture of neostigmine 0.05 mg/kg and atropine 0.02 mg/kg was injected i.v. and the effect on the suxamethonium block was observed.

Atypical esterase homozygotes. In the five patients who were atypical esterase homozygotes (one child and four adults), a bolus of suxamethonium was injected and its effect on the twitch response was observed. During recovery of neuromuscular transmission, a mixture of neostigmine 0.05 mg/kg and atropine 0.02 mg/kg was injected i.v. and its effect on
the block was observed at different degrees of desensitization.

RESULTS

Normal patients

Suxamethonium bolus injection. In five normal patients, suxamethonium 0.1 mg/kg produced partial and transient depolarizing neuromuscular block which was characterized by a sustained response to tetanus and absence of post-tetanic facilitation. When the same dose of suxamethonium was repeated after neostigmine 0.05 mg/kg, a marked potentiation of the block and delay of recovery were observed (fig. 1).

Suxamethonium infusion. In the other five normal patients, the infusion of suxamethonium 0.1% was adjusted to produce about 75% block. Initially, the block was depolarizing in nature as indicated by maintained tetanus and absence of post-tetanic facilitation. Gradually, desensitization started to develop, as shown by an increasing tetanic fade and post-tetanic facilitation. After 40–60 min, when desensitization block was established fully, the injection of neostigmine 0.05 mg/kg potentiated the block in all five patients. Cessation of the infusion was followed by recovery of neuromuscular transmission (fig. 2).

Atypical esterase homozygotes

In the five patients with atypical plasma cholinesterase activity, the effect of neostigmine on the neuromuscular block provided by suxamethonium showed marked variations. The response differed according to the type of block and degree of desensitization at the time of reversal, as assessed by tetanic fade and post-tetanic facilitation.

In one of these patients the injection of suxamethonium 0.1 mg/kg produced complete neuromuscular block which was of the depolarizing type, as indicated by maintained tetanus and absence of post-tetanic facilitation (fig. 3A). After 20 min, recovery started and was associated with early desensitization shown by partial tetanic fade. The injection of neostigmine at that time potentiated the block and delayed recovery (fig. 3B).

In the second and third patients in this group, suxamethonium 0.5 mg/kg produced complete neuromuscular block. Recovery started after 45 min and was associated with moderate desensitization. Neostigmine 0.05 mg/kg partially reversed the block (fig. 4).

In the fourth and fifth patients, suxamethonium 1 mg/kg produced complete neuromuscular block. After 90 min, recovery started and was associated with marked desensitization with complete tetanic fade and marked post-tetanic facilitation. Neostigmine 0.05 mg/kg produced an immediate and effective antagonism of the block (fig. 5).

DISCUSSION

Suxamethonium is a quaternary ammonium compound which is hydrolysed rapidly by plasma cholinesterase. The drug, consisting of two acetylcholine molecules linked together (Paton, 1959), can compete with acetylcholine for the cholinergic receptors and, like acetylcholine, will depolarize the end-plate. Initially, the depolarizing activity predominates. However, with increasing dose or time, or both, (Crul
FIG. 2. The twitch response to ulnar nerve stimulation at 0.25 Hz during the continuous infusion of suxamethonium 0.1%. About 75% neuromuscular block was maintained. The block was initially depolarizing in nature as indicated by maintained response to tetanic stimulation and no post-tetanic facilitation. Gradual desensitization occurred, with increasing tetanic fade and post-tetanic facilitation. After 45 min, desensitization block was established fully. However, the injection of neostigmine 0.05 mg/kg potentiated the block. Cessation of the infusion was followed by recovery.

FIG. 3. The twitch response to ulnar nerve stimulation at 0.25 Hz in an atypical esterase homozygote. The injection of suxamethonium 0.1 mg/kg produced complete neuromuscular block, depolarizing in nature as shown by maintained tetanus and no post-tetanic facilitation (A). Recovery started after 20 min and was associated with partial desensitization. The injection of neostigmine at that stage potentiated the block and delayed recovery (B).
et al., 1966), desensitization occurs gradually (Thesleff, 1955) and the competitive nature of the molecule is manifested. Receptor desensitization, which may begin at the moment of application of the drug and in parallel with depolarization, becomes apparent later in time because it has a slow rate of development (Gissen and Nastuk, 1970).

The present report confirms previous investigations showing that desensitization can follow absolute overdosage in patients with normal plasma cholinesterase activity whether produced by repetitive doses or by an infusion of suxamethonium; or it may follow relative overdosage in patients with atypical esterase (homozygotes) (Churchill-Davidson and Christie, 1959; Churchill-Davidson, Christie and Wise, 1960; Katz, Wolf and Papper, 1963; Vickers, 1963). Therefore desensitization block is not a cause but a result of prolonged suxamethonium block whether because of continuous administration of suxamethonium in normal patients or its delayed hydrolysis in atypical homozygotes.

Neostigmine can inhibit both plasma- and acetylcholinesterase enzymes (Irwin and Smith, 1960). Therefore its interaction with suxamethonium block may vary not only according to the type of block, but also to the plasma cholinesterase activity of the patient.

The present report has shown, in the patients with normal plasma cholinesterase activity, that neostigmine always potentiates suxamethonium block whether it is depolarizing or desensitizing. In normal patients, suxamethonium is hydrolysed by plasma cholinesterase rapidly (Kalow, 1959). Injection of neostigmine under such conditions will inhibit the plasma cholinesterase, delay the hydrolysis of suxamethonium and potentiate its neuromuscular blocking effect even when desensitization is established fully.

Gissen and others (1966) have investigated the effect of neostigmine on desensitization block following i.a. infusion of suxamethonium. They concluded that the response of the muscle to anticholinesterases in patients with normal, and perhaps atypical, plasma
cholinesterase enzymes depends on the presence or absence of suxamethonium in the blood. Neostigmine will not antagonize a desensitization block if suxamethonium is still present in the circulation (Churchill-Davidson and Katz, 1966). The present investigation, however, suggests that these findings apply only to patients with normal plasma cholinesterase activity and not to those who are homozygous for the atypical esterase.

In patients with atypical plasma cholinesterase activity, the enzyme plays no part in the elimination of suxamethonium since there is virtually no hydrolysis of the drug at the pH of blood and in the concentrations used clinically (Kalow, 1959). Under such conditions, the antiplasmacholinesterase action of neostigmine will not change the rate of hydrolysis of suxamethonium. However, the anti-acetylcholinesterase action of neostigmine will effectively increase the concentration of acetylcholine at the neuromuscular junction by decreasing its rate of hydrolysis (Nastuk and Gissen, 1965). Such an effect will potentiate the depolarizing phase of suxamethonium and yet will reverse its desensitization phase.

In atypical patients, suxamethonium produced a depolarizing block initially, followed by gradual desensitization. The present report confirms the in vitro findings of Gissen and Nastuk (1966, 1970), showing that the degree of desensitization is directly proportional to the drug concentration used. The resulting neuromuscular block will be determined by a balance between the initial depolarization and the degree of desensitization. There must be a broad spectrum where different proportions of both mechanisms co-exist (Baraka, 1972). The early use of neostigmine when depolarization predominates will potentiate the block despite the evidence of partial desensitization (Baraka, 1975b). However, when desensitization is established fully, the block can be reversed with neostigmine. The degree of reversal is not related to the magnitude of neuromuscular block, but is proportional to the degree of desensitization at the time of reversal.

It can be concluded that neostigmine may affect suxamethonium block by inhibiting both plasma and acetylcholinesterase activity. In normal patients, the inhibition of plasma cholinesterase predominates, and the block of suxamethonium whether depolarizing or desensitizing will be potentiated as a result of delayed hydrolysis. On the other hand, in patients inheriting atypical plasma cholinesterase, the anti-acetylcholinesterase activity of neostigmine will predominate. This can effectively increase the concentration of acetylcholine at the neuromuscular junction and hence potentiate the depolarizing phase of suxamethonium while antagonizing the desensitizing phase. The degree of reversal is proportional to the degree of desensitization.

REFERENCES


INTERACTION DU SUXAMETHONIUM ET DE LA NEOSTIGMINE SUR LES MALADES AYANT UNE CHOLINESTERASE NORMALE OU ATYPIQUE

RESUME
On a étudié sur 10 malades normaux et sur cinq malades ayant une activité de cholinestérase atypique du plasma, l’effet de la néostigmine à raison de 0,05 mg/kg sur le blocage neuromusculaire produit par le suxaméthonium, en enregistrant la crispation se produisant en réponse à la stimulation du nerf ulnaire. Sur les malades normaux, la néostigmine a rendu possible le blocage produit par le suxaméthonium qu’il soit du type dépolarisant ou du type désensibilisant. Par contre, sur les malades ayant une activité de cholinestérase atypique du plasma, la néostigmine a rendu possible la phase de dépolarisation du blocage par le suxaméthonium, tout en contrariant la phase de désensibilisation. Le degré d’antagonisme n’a pas été relié à l’importance du blocage neuromusculaire, mais il a été proportionnel au degré de désensibilisation au moment de l’antagonisme.