RESPIRATORY DEPRESSION FOLLOWING THE USE OF TACRINE AND SUXAMETHONIUM

A Case Report

BY

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SUMMARY

A case of prolonged respiratory depression following the use of tacrine and suxamethonium is described in a patient having normal pseudocholinesterase levels. The phase II block which developed was successfully treated by neostigmine. It is suggested that the patient may have been abnormally sensitive to the anticholinesterase action of the tacrine.

Tacrine (THA), an anticholinesterase, has been advocated as a means of safely extending the duration of action of suxamethonium and thus reducing the amount used in unit time (Gordh and Wåhlin, 1961; McCaul and Robinson, 1962; Barrow and Smethurst, 1963). By reducing the total dose of suxamethonium there is less chance of a phase II neuromuscular block supervening. On purely theoretical grounds this type of block is unlikely to occur in the presence of an anticholinesterase. This paper reports the occurrence of a dual block in the presence of tacrine and with a small total dose of suxamethonium.

CASE HISTORY

A lady aged 20 and weighing 59 kg was admitted with abdominal pain; a diagnosis of acute appendicitis was made. On clinical examination the respiratory and cardiovascular systems were both found to be normal. The blood pressure was 130/80 mm Hg and her temperature 99.6°F (37.6°C). There was no history suggestive of liver disease. A dilatation and curettage had been performed three years previously without apparent incident. No record of this anaesthetic was available.

Premedication consisted of papaveretum 10 mg and hyoscine 0.4 mg 1 hour pre-operatively. She arrived at the anaesthetic room awake but calm. After pre-oxygenation for 5 minutes induction was carried out with thiopentone 250 mg, the patient being in the head-up position. The trachea was intubated following the injection of suxamethonium 50 mg. Anaesthesia was maintained with nitrous oxide (70 per cent) and oxygen (30 per cent) using a Manley non-rebreathing ventilator. The minute volume was 10 l/min. The effect of the initial dose of suxamethonium wore off in just under 6 minutes as judged by a Wakeling peripheral nerve stimulator. Tacrine 15 mg, suxamethonium 20 mg and atropine 0.6 mg were then injected. Further 20 mg doses of suxamethonium were given 16, 25 and 31 minutes later. The nerve stimulator was used throughout as a guide to muscular repolarization. Halothane and pethidine were not used during the anaesthetic. During insertion of the skin sutures very slight movement of the eyelids was observed.

Fifteen minutes after completion of the operation, which was uneventful and lasted 48 minutes, the patient's spontaneous respiratory minute volume was inadequate, being only 3.2 l/min, as measured by Wright Respirometer. Ventilation was reinstituted with nitrous oxide and oxygen. Post-tetanic facilitation was thought to be present at this time and the patient showed no signs of regaining consciousness. One hour later the spontaneous minute volume was still only 3.2 l/min, but now there was marked post-tetanic facilitation. A diagnosis of a phase II block was made. In view of the unusual circumstances no effort was made to reverse the block before consultation with another anaesthetist. When the diagnosis was agreed atropine 1 mg and edrophonium 10 mg were injected intravenously. Two and a half minutes later the patient coughed violently and became very active. The tube was removed and the patient spoke immediately. At this time neostigmine 2.5 mg was injected intravenously. She was able to lift her head off the pillow and move all her limbs. After half an hour the patient's condition remained perfectly satisfactory and stable and she was returned to the ward. After 4 hours, when pulse, blood pressure and muscular power were still normal, observations were discontinued.

On the following day she complained of pain in the shoulders, neck and arms, but had no recollection of any of the events which occurred in the operating theatre. The plasma pseudocholinesterase level was estimated and found to be normal at 80 units per 100 ml (method of Biggs, Carey and Morrison, 1958).
DISCUSSION

The important points in this report are: the total amount of suxamethonium used was only 130 mg; no respiratory depressant drugs (other than premedicants and thiopentone) were administered; improvement of the patient was dramatic following administration of an anti-acetylcholinesterase (confirming the diagnosis of a phase II block as the cause of the respiratory depression); the response to the initial dose of suxamethonium before tacrine was administered was normal.

Abnormal responses to suxamethonium have been classified by Bush (1961) into phase II block, occurring after administration of doses exceeding 1 g, extended response, and prolonged response. The second and third types can occur after single doses of suxamethonium in patients with reduced or atypical pseudocholinesterase levels.

The case now reported does not resemble any of these types. In particular the quantity of suxamethonium given was low (130 mg) and the effect of the initial dose lasted only 6 minutes, which must be accepted as a normal figure. Furthermore, the only pharmacological treatment of a phase II block is to give an anticholinesterase. It is difficult to see quite how this type of block occurred when tacrine, itself a weak anticholinesterase, had already been given.

A possible explanation for this occurrence lies in the fact that tacrine has multiple anti-enzyme activities, being an anticholine-acetylase, as well as an anticholinesterase (de la Lande and Bentley, 1955; Shaw and Bentley, 1953). As an anticholinesterase it would be expected to cause marked bradycardia due to its effect in potentiating the muscarinic actions of acetylcholine, but in practice this effect is more marked with other anticholinesterases. Two points to be considered are that tacrine is a much more potent inhibitor of pseudo- (or butyryl) cholinesterase than of acetylcholine esterase and that, by its anticholineacetylase effect, it may reduce the amount of acetylcholine available at the endplate region after the suxamethonium has been removed. In these circumstances the administration of edrophonium would increase the available acetylcholine and restore normal transmission at the neuromuscular junction.

The effects postulated may well occur to some degree in all patients to whom tacrine is given. If the drug were to have an enhanced effect as an anticholine-acetylase in certain individuals, then it could be expected that a serious reduction in available acetylcholine would produce an apparent non-depolarizing block. The human choline-acetylase enzyme system has not been investigated to the same extent as the pseudocholinesterase system, but it is a reasonable assumption that there must be a quantitative distribution throughout the population, some people having a higher level than others. Clinically important quantitative differences in the activities of some other acetylase systems, such as that producing inactivation of isoniazid, are already well documented (see Kalow, 1962, for references). The anticholine-acetylase activity of tacrine would be more apparent in those individuals whose enzyme levels were at the lower end of the distribution curve. Whether or not the above assumptions are correct, there is little doubt that tacrine caused the trouble in the case reported here.

There are several other cases of postoperative respiratory depression following the use of tacrine reported in the literature. In the series described by Barrow and Smethurst (1963) the overall incidence of respiratory depression was 2 per cent. One of us (P.O.) has now used tacrine on 107 occasions, and in addition to this case there was one other in which there was difficulty in re-establishing respiration postoperatively, the circumstances on that occasion being very similar to the case now described. It is possible that the complication occurred in individuals who are more than normally sensitive to the anticholine-acetylase action of tacrine. It is believed that this case report and the explanation given for the respiratory depression may be important in indicating that tacrine, far from giving protection from the development of phase II block, may in certain patients actually promote one. An incidence of respiratory depression of 1:50 (2 per cent) when using suxamethonium and tacrine combined is far greater than the incidence following the use of the former alone.

If this hypothesis is correct, then any patient showing evidence of phase II block after the administration of tacrine may be treated satisfactorily with neostigmine. This knowledge would remove an important objection to what is otherwise a very safe way of prolonging the effect of suxamethonium.
RESPIRATORY DEPRESSION AFTER TACRINE AND SUXAMETHONIUM

REFERENCES


DEPRESSION RESPIRATOIRE APRES L'USAGE DE TACRINE ET DE SUXAMETHONIUM: UNE OBSERVATION

SOMMAIRE

On décrit un cas de dépression respiratoire prolongée après l'administration de tacrine et de suxaméthonium chez un malade ayant des taux normaux de pseudo-cholinestérase. Le bloc de la phase II qui s'était développé a été traité avec succès par la néostigmine. On suggère que le malade a pu être anormalement sensible à l'action anticholin-acétylase de la tacrine.

ATEMDEPRESSION NACH ANWENDUNG VON TACRINE UND SUXAMETHONIUM: EIN FALLBERICH

ZUSAMMENFASSUNG

Es wird über einen Fall von verlängerter Atemdepression nach Anwendung von Tacrine und Suxamethonium berichtet. Der aufgetretene Block (Phase II) wurde mit gutem Erfolg mit Neo-stigmin behandelt. Es wird angenommen, daß der Patient möglicherweise auf die Anticholinázetylase-wirkung des Tacrine übermäßig empfindlich reagierte.