SERUM CHOLINESTERASE IN ANAESTHESIA WITH REFERENCE TO NEOSTIGMINE, FENTANYL, AND DIHYDROBENZPIRIDOL

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NEOSTIGMINE is used extensively to antagonize blockade of neuromuscular transmission produced by curare or gallamine. This effect is achieved by increasing the release of acetylcholine at the prejunctional site, by combining with the enzyme acetylcholinesterase at the neuromuscular junction, and probably also by direct action on skeletal muscle. Inhibition of serum cholinesterase (E.C. 3.1.1.8., pseudocholinesterase) also occurs, but this plays a very minor role in producing the effect for which neostigmine is usually administered. However, since this enzyme is related to the distribution of the drug within the body, it was of interest to measure the effect of neostigmine administered at the termination of surgery on genetically normal serum cholinesterase activity.

METHOD

Patients were premedicated with morphine or meperidine, atropine or scopolamine, and alternative anaesthetic techniques were applied. Both utilized a thiopentone succinylcholine induction, followed by curare to maintain muscular relaxation, and ventilation of approximately 50 per cent in excess of the Radford nomogram value. Anaesthesia was continued using halothane and nitrous oxide, or nitrous oxide and intermittent injections of fentanyl and droperidol. Blood samples were obtained as atraumatically as possible prior to induction, prior to administration of neostigmine, and ten and forty minutes later. Atropine 1.2 mg. was injected 2 minutes prior to neostigmine. All sampling took place between 7 A.M. and 2 P.M.

Serum cholinesterase was determined by the method of Kalow and Genest,¹ using the substrate benzoylcholine chloride. The change in absorbance at 240μ when serum and substrate are incubated for 4 minutes at 30° C. is a measure of cholinesterase activity. The normal range by this method is 80–150 units.

RESULTS

The changes in serum cholinesterase activity 10 minutes following neostigmine injection are shown in Figure 1. Figure 2 represents the return of cholinesterase activity 40 minutes after administration by relating the cholinesterase activity prior to drug administration to the cholinesterase activity 40 minutes later, expressed as a percentage of the original value. Table I gives details of the changes in enzyme activity that occurred during surgery, and Table II relates age to preinduction enzyme activity.

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FIGURE 1. Each vertical line represents the reduction in serum cholinesterase activity that had occurred in each patient ten minutes following neostigmine administration.

FIGURE 2. Ordinate: Serum cholinesterase activity forty minutes after neostigmine administration expressed as percentage of activity prior to injection of drug. Abscissa: Serum cholinesterase activity prior to neostigmine administration.

TABLE I

Serum Che. activity at induction	Surgery	Dura- tion (min.)	Anaesthesia	Blood transfusion	Che. activity at termination
100	abdominal perineal resection	165	thiopentone, N ₂ O, fentanyl, droperidol, curare	1000	102
101	thoracotomy	105	"	—	103
39	Roux en Y anastomosis	135	"	—	50
69	pyloroplasty	165	"	—	75
87	femoral popliteal bypass	205	"	500	90
106	cholecystectomy	155	"	—	105
101	cholecystectomy	160	"	—	97
99	McMurray osteotomy	105	"	500	105
79	breast biopsy	45	"	—	84
89	abdominal hysterectomy	95	"	—	91
67	laparotomy	95	"	200	77
155	spinal fusion	140	"	500	145
41	nephrectomy	170	"	2500	53
132	herniorrhaphy	80	"	—	116
65	portocaval shunt	320	"	2000	72
65	hip plating	180	"	500	63
68	repair detached retina	105	thiopentone, N ₂ O, halothane, curare	—	65
63	enucleation	60	"	—	55
96	gastrectomy	210	"	1500	82
54	cholecystectomy	210	"	1000	63
39	gastrectomy	175	"	500	39
177	gastrectomy	145	"	—	136
88	colectomy	145	"	500	93

TABLE II

Age (years)	Serum Che. activity (units)	Age (years)	Serum Che. activity (units)
50	41		
48	69	86	39
45	132	85	39
43	137	76	68
40	67	75	87
39	77	74	88
34	177	73	54
34	97	69	63
33	89	67	100
32	107	66	96
29	101	64	99
26	155	62	101
24	65	58	111
24	106	56	65
21	79	54	72

DISCUSSION

It appears from the cases presented that neostigmine in clinical dosage can sometimes reduce cholinesterase activity to a low level. In common with all enzymes, serum cholinesterase activity reflects the presence or absence of inhibitors, activators, and cofactors. It is also well recognized that activity may be increased or decreased in a variety of clinical entities. Age and sex as factors affecting the enzyme have not been clearly elucidated.^{2,3} A variation with age is shown here (Table II), but other reasons for low values at induction have to be taken into consideration. These include liver dysfunction, macrocytic anaemia, and a variety of acute debilitating febrile diseases, as well as pregnancy and labour.⁴

Apart from drugs that have a direct depressant effect on liver function, a number of compounds have been shown to have an inhibitory effect on serum cholinesterase activity, including chlorpromazine⁵ and a variety of narcotic analgesics and their antagonists.⁶ The inhibitory effect of phospholine iodide eye drops has been described by Osserman,⁷ and clinical studies have been reported by other workers.^{8,9} The low preinduction level of the enzyme in one of our patients was associated with the use of this drug, and it is noteworthy that 150 minutes after the administration of neostigmine the enzyme activity was still only 47 per cent of the original value, which was 63 units.

The changes that occurred during surgery were small except in one case, and insufficient data is available for a definite explanation. Blood transfusions varying from 500 to 2,500 ml. played no apparent part in altering enzyme activity, and this agrees with the *in vitro* findings of Fromberg and his colleagues.¹⁰

Although the findings during general anaesthesia did not suggest that fentanyl and droperidol possessed a significant effect on the enzyme activity *in vivo*, the use of these drugs for sedative purposes during local anaesthesia encouraged confirmation of this hypothesis. Blood samples were taken from patients receiving no drugs other than fentanyl and droperidol, the results being shown in Table III. With the method described, there appeared to be no appreciable effect upon the enzyme activity.

Thus it seems that a low or subnormal serum cholinesterase activity may not be unusual in the surgical patient, particularly in the geriatric range, and a therapeutic dose of neostigmine can further reduce this activity. This occurrence might have a clinically significant effect on the quantity of any neostigmine administered subsequently that would be sufficient to produce depression of neuromuscular transmission, and on the inactivation of those drugs affected by this enzyme.

SUMMARY

The activity of serum cholinesterase has been measured prior to and following surgery in patients anaesthetized with a nitrous oxide, fentanyl, droperidol, or halothane technique. Except in one case no significant changes occurred. Neostigmine reduced enzyme activity to a low level in some patients. This occurrence might have a clinically significant effect on the quantity of any neostigmine

TABLE III

Age (years)	Weight (kg.)	Serum Che. activity	Drugs	Duration of injection (min.)	Delay before sampling (min.)	Pseudo-che. activity
54	59	72	fentanyl droperidol 10 mg.	4	3	77
43	68	137	fentanyl droperidol 10 mg.	4	3	130
34	50	97	fentanyl droperidol 10 mg.	4	3	103
39	63	77	droperidol 10 mg.	4	3	76
58	77	111	fentanyl droperidol 10 mg.	4	3	106
32	61	107	droperidol 10 mg.	4	3	106
30	57	139	droperidol 10 mg.	4	3	137
27	69	132	droperidol 10 mg.	4	3	134

administered subsequently that would be sufficient to produce depression of neuromuscular transmission, and on the rate of inactivation of those drugs affected by this enzyme.

RÉSUMÉ

On a mesuré l'activité de la cholinestérase du sérum avant et après l'opération chez des malades anesthésiés au protoxyde d'azote, au fentanyl, au dropéridol ou à l'halothane. On n'a noté aucun changement sauf dans un cas. La néostigmine a diminué considérablement l'activité de cette enzyme chez quelques malades. Cette éventualité pourrait avoir un effet clinique important d'abord sur la dose de néostigmine qui serait administrée subséquemment et qui serait suffisante pour produire une dépression de la transmission neuromusculaire, puis sur le taux de diminution d'activité des médicaments influencés par cette enzyme.

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