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Pharmacokinetic Basis for the Dose-dependent Decline in the Neuromuscular Blocking Effect of Gallamine

To the Editor:—Gallamine triethiodide is a neuromuscular blocking drug that has been used clinically for more than three decades. Direct experimental evidence for a dose-dependent decline in the neuromuscular blocking effect (skeletal muscle paralysis) of gallamine in humans is available from the data of Walts and Dillon,[1] as shown in figure 1. It can be seen that muscle paralysis declines at an essentially constant rate, but the rate of decline (or recovery from paralysis) decreases with increasing gallamine bolus dose.

That the dose-dependent decline in the pharmacologic effect of gallamine is related to its pharmacokinetic properties is evident from an examination of the relationship between the rate of decline of neuromuscular paralysis and the apparent rate of decline of (log) gallamine plasma concentration over the same effect range. Walts and Dillon[1] provided pharmacodynamic (effect–time) data for different doses of gallamine from which the average rate of decline of effect can be calculated by linear regression (fig. 1). These authors, however, did not measure gallamine plasma concentrations. The pharmacokinetics (plasma concentration–time profiles) of gallamine have only recently been fully characterized in surgical patients[2] at doses comparable to that used to generate the pharmacodynamic data. Using average pharmacokinetic parameters for gallamine,[2] plasma concentrations of the drug corresponding to the various degrees of muscle paralysis reported by Walts and Dillon[1] can be predicted. These concentrations allow the estimation of the apparent rate of decline (k_{app}) of (log) plasma gallamine concentration over the paralysis range observed with each dose of gallamine. A plot of the average rate of decline of gallamine-induced muscle paralysis as a function of the calculated k_{app} for three doses of gallamine is presented in figure 2. There

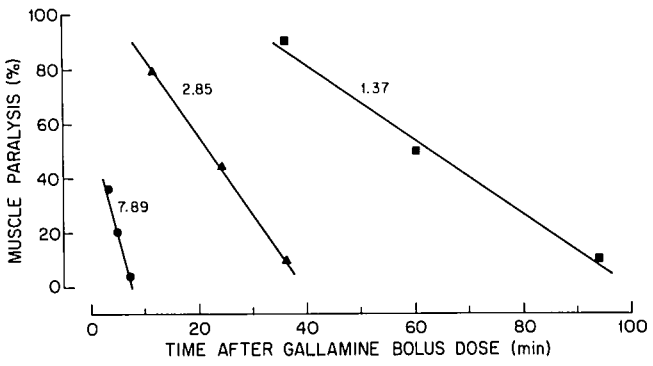

FIG. 1. Pharmacologic effect–time data reported by Walts and Dillon,[1] showing the dose dependence of the rate of decline of the neuromuscular blocking effect (muscle paralysis) of gallamine in humans following three (●—32.2 mg or 18 mg/m^2; ▲—56.5 mg or 36 mg/m^2; ■—128 mg or 72 mg/m^2) different bolus doses of the drug. Each point represents the median value from 20 patients undergoing general anesthesia, while the solid lines represent the linear regression lines. The numbers next to each set of data are the average rates of decline of the neuromuscular paralysis (per cent per min), obtained by linear regression.

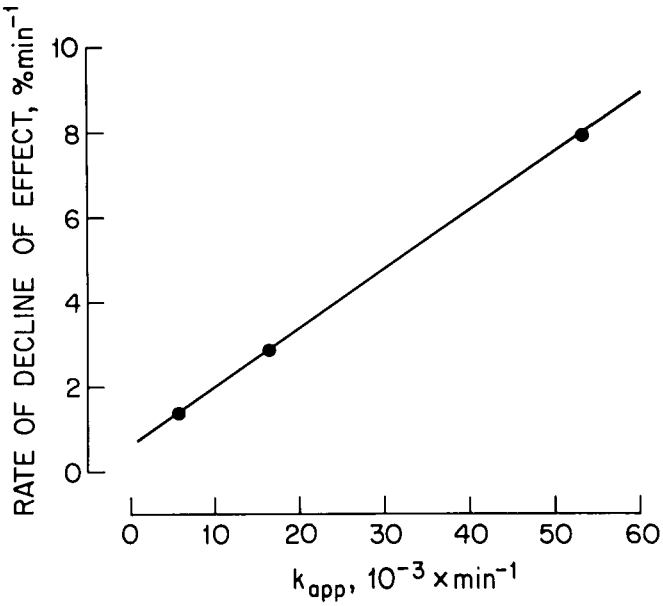

FIG. 2. Relationship between the rate of decline of the neuromuscular blocking effect of gallamine and the apparent rate of decline of (log) plasma gallamine concentration over the same effect range (k_{app}). Individual data points represent data from each dose of gallamine used, while the solid line represents the linear regression line ($r^2 > 0.99$, $P < 0.001$). $k_{app} = 2.3 \log Cp_{max} - \log Cp_{rec}/t$ where Cp_{max} and Cp_{rec} represent gallamine plasma concentrations at maximum (peak) paralysis and at recovery, respectively, and t represents the time interval between these two degrees of paralysis.

is an excellent linear relationship between these two variables, demonstrating that the rate of decline of (or recovery from) the neuromuscular blocking effect of gallamine is controlled by the rate at which gallamine plasma concentration declines during a particular effect range. This relationship reflects the progressively changing contribution of drug distribution and elimination, respectively, to the decline of gallamine effect as relaxant dosage is increased. When the dose is small, peak plasma concentration is low (as is the peak paralysis produced), and decline below the threshold concentration for neuromuscular blockade occurs during the distributive phase. The decline of effect is thus more rapid. As the dose of gallamine is increased, higher gallamine concentrations are reached in plasma and the decline to threshold concentration occurs during the slower elimination phase. Hence, the rate of recovery from paralysis is lower.

The approach presented here to explain the dose-dependent decline in the pharmacologic effect of gallamine is not new. In fact, the theory underlying the present explanation was proposed more than a decade ago and utilized to explain the dose-dependent decline in the neuromuscular blocking effect of the classical skeletal muscle relaxant drug *d*-tubocurarine.[3] More recently an analogous explanation has been proposed for the dose-dependent duration of action of intravenous anesthetic fentanyl.[4] The explanation for gallamine presented here is possible, since both pharmacodynamic and pharmacokinetic data are now available for gallamine.

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Reduction of Postlumbar Puncture Backache by the Use of Field Block Anesthesia prior to Lumbar Puncture

To The Editor:—Backache is a common postoperative complaint following any type of anesthesia. The incidence of immediate postoperative localized backache is 2–31%.[1,2] It is usually characterized by marked tenderness of the lumbar spinous area. The etiology of backache associated with lumbar puncture is due to localized trauma, which leads to aseptic periosteitis, tendonitis, inflammation of the ligaments, and osteochondritis. Among these patients, about 3% of cases might suffer backache for prolonged periods (table 1). One way of preventing this complication is by the use of field block anesthesia as described by Wilkinson.[3] We would like to present a series of cases in which there was no prolonged localized backache, since the inception of this new technique in May 1983 (table 1). This is in comparison to the 2.73% incidence of chronic backache in our own previous series of 2,046 lumbar punctures in the last 5 years ($P < 0.001$). There were eight spinal anesthetics and 256 epidural anesthetics performed on obstetric patients, and 58 epidural anesthetics on surgical patients preceded by the "field block" technique since May 1983. Prior to this, only infiltration anesthesia of the skin and ligaments were performed for the insertion of the needle.

The method of field block as originally described by Wilkinson[3] was modified slightly as follows:

A skin wheal is raised over the site of puncture with a 25-gauge needle, with the use of 0.2 ml of 0.5% bupivicaine. A 3.8 cm needle is used to deposit 1.0 ml of 0.5% bupivicaine bilaterally into the interspinous space near the lamina. This method is able to fully anesthetize the recurrent spinal nerves, which innervate the interspinous ligaments and muscles (see fig. 1).

TABLE 1. Comparison of Incidence of Transient and Prolonged Localized Backache in Two Groups of Patients

	Without Spinal Nerve Block	With Spinal Nerve Block	*P*
Number of cases	2,046	322	
Transient backache (less than 3 days)	286 (13.97%)	18 (5.59%)	<0.05
Prolonged backache (over 3 months)	56 (2.78%)	0 (0%)	<0.001