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TITLE: OPTIMIZING DOSING OF ATRACURIUM TO ALLOW FOR VARIATION IN BODY SOMATOTYPE

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Studies have found little correlation between a dose of a muscle relaxant based on total body weight (TBW) and the degree of neuromuscular blockade. The aim of this study was to compare the accuracy of dosing atracurium using different patient parameters, including TBW, height (Ht), body surface area (BSA), and lean tissue mass (LTM), and the administration of a fixed dose in patients of varying body somatotype.

After institutional approval and informed consent, 80 patients were studied. LTM was calculated using the method of James, and BSA by method of Dubois. Patients were grouped according to their estimated body fat content (BF%). Atracurium was infused by a programmed profile which was scaled by patient LTM, with frequent arterial sampling during the first hour. Atracurium plasma concentration was later determined by an HPLC assay. Accuracy of dosing was assessed by the bias and absolute prediction error (APE) between the plasma concentrations achieved in the different BF groups and that of the 25% BF group. Dosing by TBW, Ht, BSA, and the administration of fixed dose were generated by linear simulation.

The results are summarised in Table 1. There was a significant skew in the bias between the different BF groups only for dosing by TBW. The overall APE was significantly smaller for dosing by LTM compared to all the other parameters.

The simulation of dosing by different patient parameters allows a direct comparison which may otherwise be impossible due to the large number of patients required. The simulations are valid for atracurium as its pharmacokinetics are linear over the concentration range that was simulated.[1] It is concluded that dosing of atracurium should be by LTM as it minimised both interpatient variability, as assessed by the overall APE, and bias due to variations in body somatotype. TBW can be considered the worst patient parameter for individualising drug dosing.

Reference 1. Br J Anaesth 55: 39S-46S, 1983.

Table 1. Mean bias(%) vs Patient dosing parameter

BF(%)	No.	LTM	TBW*	Ht	BSA	FIXED
<17	10	-2.6	-13.3	7.7	-1.2	-0.3
18-22	12	-1.5	-7.1	12.9	3.7	9.3
23-27	20	0	0	0	0	0
28-32	12	2.2	-1.5	-0.9	0.6	-1.9
33-37	10	1.1	17.5	-5.9	3.1	-8.9
38-42	8	-2.3	23.4	-6.6	4.9	8.78
>43	8	-0.7	41.4	3.1	16.9	5.1
APE(%)	80	17.5#	21.9	23.3	19.6	20.4

* one-way ANOVA, $p<0.05$

\# Student's t test with Bonferroni correction, $p<0.05$

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TITLE: RESISTANCE TO ATRACURIUM IN MUSCLES UNDER THERMALLY INJURED SKIN IN THE RAT

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In thermal injury, both humans and rats demonstrate resistance to nondepolarizing muscle relaxants (NDMR). This resistance is proportional to the body surface area (TBSA)[1] burned with little or no effect in burns less than 25% TBSA. Resistance usually peaks at 4-5 weeks post injury with little resistance at one week[1,2]. Resistance to NDMR has usually been studied in skeletal muscles distant from burned areas. The object of this study was to examine the effect of small burns (approximately 2% TBSA) on function of NDMR on muscles under the burned skin.

METHODS: The experiments were carried out with the approval of the institutional animal care committee. All thermal injuries were performed by exposure to boiling water for 8 seconds in shaved animals anesthetized with 45 mg/kg of phenobarbital who received analgesia (butorphenol) post injury. Group I was unburned controls, Group 2 had a 40% TBSA burn which did not include the area over the gastrocnemius, Group 3 had casts placed on their left leg to provide immobility, Group 4 - 2% TBSA burn over the left gastrocnemius. At 1 and 2 and 4 weeks post injury, animals were anesthetized, had their gastrocnemious muscle and nerve exposed, the Achilles tendon attached to a force transducer and supramaximal electrical D. C. stimulation applied to the nerve. The % twitch depression to an intravenous bolus of 1.5 mg/kg of atracurium was determined.

RESULTS:

Group	injury	n	mean % twitch depression	±SE
1	controls	10	96.2	3.2
2	40% 1 wk	9	83.9	4.3
	40% 2 wk	9	49.8	10.1
	40% 4 wk	6	29.5	9.2
3	cast	7	58.6	9.3
4	2% 2 wk	6	5.2	3.1
	2% 2 wk	10	6.0	2.0
	2% 4wk	4	76.3	10.3

The muscle under the burned skin has profound resistance after only one week, while the muscles not under the injured area but from animals with 40% TBSA burns showed no resistance at that time. At four weeks, 40% TBSA produces 29.5% twitch depression in skeletal muscle distant from burned skin. Casted animals demonstrated that immobility resulted in a small amount of resistance but not nearly enough to account for that seen with the small burn. Ligand binding with α-bungarotoxin showed that at 2 weeks, acetylcholine receptors under the burned skin were 4 times as dense as in the gastrocnemious in the contralateral uninjured leg in Group 4.

CONCLUSION: Muscles under small TBSA burns show profound resistance to NDMR one week post injury. Our findings may have clinical relevance. NDMR are often utilized to provide optimal conditions for endotrachael intubation. Facial burns may be associated with resistance to critical muscles underneath the burned skin such as the masseters at a time when resistance to NDMR is unexpected in patients with small TBSA burns (<25%) or at 1 week post injury.

REFERENCES: 1. Anesthesiology 65:517, 1986
2. Anesthesiology 69:696, 1988

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