one of whom reported palpitations for 30 minutes on every experimental day (table IV).

Discussion

These results show that ibuterol hydrochloride in the doses given relieves bronchial obstruction in asthma without causing circulatory effects. The equivalent weights of ibuterol hydrochloride and terbutaline sulphate are 402 and 274 respectively. Thus 2 mg ibuterol hydrochloride corresponds to 1.36 mg terbutaline sulphate, and after hydrolysis this dose of ibuterol hydrochloride has the same bronchodilating effect during the first three hours after administration as a single 5-mg dose of terbutaline sulphate.

Ibuterol hydrochloride thus seems to produce a bronchodilating effect that is more than three times that of terbutaline sulphate during the first three hours after administration. This ratio of activity is somewhat greater than the ratio reported for circulatory effects by Höglund *et al.*⁷ Moreover, the differences in spirometric response during the first two hours indicate that ibuterol hydrochloride has a faster onset of action than terbutaline; this agrees well with the observations of Höglund *et al.*⁷

The therapeutic response to a dose of ibuterol hydrochloride

by mouth indicates that one of the basic ideas behind the "pro drug" concept is fully achieved⁸; by using ibuterol hydrochloride as a pro drug to terbutaline an increased degree of utilisation of the generated amount of terbutaline is achieved. This leads us to believe that ibuterol hydrochloride may be more effective in the treatment of asthma and bronchitis than terbutaline. Further investigations will be needed to confirm this.

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Value of determination of oxygen consumption in tetanus*

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Summary

Oxygen consumption ($\dot{V}O_2$) was determined in 10 patients with moderate tetanus. The mean ($\pm$ SE) $\dot{V}O_2$ of 425.2 ± 50.3 ml/min on admission fell significantly to 249.9 ± 13.1 ml/min standard temperature and pressure dry (STPD) after parenteral diazepam. There was also a significant fall in minute ventilation after administration of diazepam. The results suggest that the simple practical determination of $\dot{V}O_2$ will be of immense value in assessing the efficacy of muscle relaxants, assessing the severity of tetanus, and determining the calorie needs of patients.

Introduction

For many years the effectiveness of sedatives with muscle relaxant and anticonvulsant properties in tetanus has been assessed by measuring interdigital distance,¹ and by morbidity and mortality statistics.²⁻⁵ These methods of assessment, while acceptable in tropical medical practice, have many shortcomings. We have measured oxygen consumption ($\dot{V}O_2$) before and after the administration of diazepam in patients with tetanus, and we report here the results that have encouraged us

to recommend the measurement of $\dot{V}O_2$ in assessing drugs with muscle relaxant properties in tetanus.

Patients and methods

Ten patients with moderate tetanus were studied as soon as they reached hospital. They had trismus with hypertonicity of chest wall and abdominal muscles as well as infrequent spasms. Expired gas was collected through a non-return valve system over five minutes into a 150-litre Douglas bag. The latter was connected to a standard volume gas meter and oxygen (Taylor Servomex (type OA 272)) and carbon dioxide (infrared gas analyser, Analytical Development Co Ltd) analysers previously calibrated with known gas mixtures. Oxygen consumption was derived from a product of minute ventilation ($\dot{V}_E$) and oxygen extraction. Values of $\dot{V}O_2$ and $\dot{V}_E$ were corrected to standard temperature and pressure dry (STPD) and body temperature and pressure saturated (BTPS) respectively. The respiratory quotient (R) was calculated from $\dot{V}CO_2/\dot{V}O_2$. The patients later received parenteral diazepam (Valium) in doses of 5 to 60 mg. After 15 minutes expired gas samples were again collected.

The energy expenditure of the patient with the highest $\dot{V}O_2$ (case 8) was calculated assuming that 1 litre of $\dot{V}O_2$ was equivalent to 0.02 MJ (5 kcal) and that the measured value of $\dot{V}O_2$ during the five minute collection period (pre-diazepam) was constant for the whole day. Predicted $\dot{V}_E$ was derived from the formula: $\dot{V}_E$ (l/min BTPS) = $22 \dot{V}O_2$ (l/min) + 2.⁶ Oxygen consumption was also determined among 12 laboratory staff (8 men and 4 women) in a supine resting state three hours after a meal.

Results

In table I the age, sex, weight, and $\dot{V}O_2$ before and after diazepam are shown. The mean ($\pm$ SE) $\dot{V}O_2$ on admission (425.2 ± 50.3 ml/min) fell after parenteral diazepam to 249.9 ± 13.1 ml/min (t paired = 3.79; $P < 0.005$). The fall in $\dot{V}O_2$ was paralleled by a concomitant fall in $\dot{V}_E$. The mean $\dot{V}_E$ of 15.4 ± 1.25 l/min fell to 10.4 ± 0.37 l/min after parenteral diazepam (t paired = 4.54; $P < 0.001$). The differences between the mean predicted values of $\dot{V}_E$ and the observed values were highly significant (table II). The $\dot{V}O_2$ values before and after

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TABLE I—Physical characteristics and $\dot{V}O_2$ and $\dot{V}E$ levels in patients with tetanus

Case No	Age and sex	Weight (kg)	$\dot{V}E$ (l/min BTPS)		$\dot{V}O_2$ (ml/min STPD)		% Fall in $\dot{V}O_2$	Dose and route of diazepam
			Before diazepam	After diazepam	Before diazepam	After diazepam		
1	28 M	60.7	15.9	11.3	320	268	16	20 mg IV
2	30 M	61.4	19.4	11.4	581	253	56	20 mg IV
3	65 M	—	13.0	9.9	395	255	35	15 mg IV
4	22 M	65.0	16.1	11.4	436	324	26	10 mg IV
5	35 M	64.0	15.6	10.1	380	240	37	10 mg IV
6	18 F	46.4	8.8	9.8	320	263	18	10 mg IV
7	40 F	58.6	21.7	10.3	577	225	61	60 mg IM
8	65 F	56.4	18.9	11.4	735	287	61	20 mg IV
9	35 F	40.4	11.3	7.6	265	175	34	10 mg IV
10	70 F	—	12.8	10.8	243	209	14	5 mg IV
Mean $\pm$ SE	40.8 $\pm$ 6.0	—	15.4 $\pm$ 1.25	10.4 $\pm$ 0.37	425.2 $\pm$ 50.3	249.9 $\pm$ 13.1	35.7 $\pm$ 5.74	—

IV = Intravenously. IM = Intramuscularly.

TABLE II—Mean values ($\pm$ SE) of measured and predicted $\dot{V}E$

	Measured $\dot{V}E$	Predicted $\dot{V}E$	<i>r</i> Paired	P
Before diazepam	15.4 $\pm$ 1.25	11.4 $\pm$ 1.1	5.19	<0.001
After diazepam	10.4 $\pm$ 0.37	7.5 $\pm$ 0.3	11.47	<0.001

diazepam were expressed in ml/min⁻¹/kg body weight⁻¹ among eight patients whose weights were known (table III). The mean $\dot{V}O_2$ fell after diazepam (*t* paired = 3.7; *P* < 0.01). In case 8 a $\dot{V}O_2$ of 13 ml/min⁻¹/kg body weight⁻¹ fell by 61% after 20 mg of intravenous diazepam (table I). Assuming 1 litre of $\dot{V}O_2$ to be equivalent to 0.02 MJ (5 kcal) the energy expenditure of this patient amounted to 22.12 MJ (5292 kcal) a day.

Table II also shows the values of $\dot{V}O_2$ for our laboratory staff, supine, resting, but awake. It was clear that the administration of diazepam brought the $\dot{V}O_2$ of patients with moderate tetanus closer to normal resting values. There was a significant correlation between $\dot{V}E$ and $\dot{V}O_2$ before diazepam (*r* = +0.79; *P* < 0.01) and after medication (*r* = 0.73; *P* < 0.05; table I). Carbon dioxide output paralleled oxygen consumption and the respiratory quotients (*R*) for the 10 patients before and after medication varied from 0.7 to 1.0.

TABLE III—Mean values ($\pm$ SE) of $\dot{V}O_2$ in patients with tetanus and normal subjects

	Patients with tetanus (n = 8)	Normal subjects, supine, resting, and awake	
		Men (n = 8)	Women (n = 4)
Mean age	34.1 $\pm$ 5.1	28.7 $\pm$ 2.2	23.2 $\pm$ 1.5
$\dot{V}O_2$ (ml/min ⁻¹ /kg ⁻¹):			
Before diazepam	7.95 $\pm$ 0.95	3.13 $\pm$ 0.15	3.05 $\pm$ 0.18
After diazepam	4.53 $\pm$ 0.24		

Discussion

Our results encourage us to recommend the measurement of $\dot{V}O_2$ in patients with tetanus as a practical and simple method of assessing the efficacy of sedatives with muscle relaxant effects and quantifying the severity of the disease. We were impressed by the substantial falls in $\dot{V}O_2$ after medication with diazepam (*P* < 0.005; table I). $\dot{V}O_2$ should be measured only in patients with moderate tetanus, as those with severe tetanus are difficult to study because pronounced trismus prevents correct insertion of the mouth-piece and the procedure often triggers severe

muscular spasms. Tight-fitting face masks may overcome this risk, but we have not been able to avoid air-leakage.

Measuring $\dot{V}O_2$ in tetanus offers quicker results on the efficacy of drugs with muscle relaxant effects than the use of mortality statistics, which suffers from the obvious weakness that the roles of several variables contributing to death, such as the age of the patient, period of onset, quality of nursing and medical care, and interfering complications, cannot be evaluated easily.

There was significant correlation between oxygen consumption and ventilation before and after diazepam. The measured $\dot{V}E$, which was also significantly greater than the predicted value, can be explained by sympathetic overactivity in tetanus.⁷ Patients with tetanus have disproportionately large rises in cardiac output compared with the rise in $\dot{V}O_2$,^{8,9} which means that oxygen extraction by the tissues or arteriovenous oxygen tension difference ($P_{aO_2} - P_{vO_2}$) will be small. This feature explains the mildness of hypoxaemia in the disease.¹⁰

One patient (case 8) had a $\dot{V}O_2$ of 13 ml/min⁻¹/kg⁻¹ before diazepam. This result is highlighted because the value was more than four times the $\dot{V}O_2$ of our resting awake laboratory staff. Furthermore, her energy expenditure of 22.12 MJ (5292 kcal) a day provided useful information for dietary management of tetanus, since this daily energy expenditure in a patient with moderate tetanus is more than twice the value for the average male Lagosian (8.4 MJ (2010 kcal)) and more than three times the value for the average female Lagosian (6.7 MJ (1610 kcal)).¹¹

In conclusion, our data show that the simple determination of oxygen consumption is valuable not only in assessing the efficacy of drugs with muscle relaxant properties but also in assessing the severity of tetanus and determining the calorie needs of patients.

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