FURTHER OBSERVATIONS ON RESPIRATORY FLOW-VOLUME LOOPS: CLINICAL EVALUATION OF A NEW ORAL BRONCHODILATOR, CP-12,521-1*

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PRESSURE, VOLUME, AND FLOW DATA obtained during spirometry and plotted as pressure-volume or flow-volume loops have been used in the study of respiratory mechanics. Pressure-volume loops are used for the display of data generated in the measurement of static and dynamic compliance of the lungs and/or chest wall.¹⁻³ Flow-volume loops have been used for the quick pattern-recognition of various pulmonary diseases⁴⁻⁶ and in the evaluation of the effects of drugs on the lower airways.^{7,8}

Based on a technical modification⁹ of the original method described by Fry and Hyatt, we evaluated a new oral bronchodilator, CP-12,521-1 (Fig. 1) in the management of patients with asthma.

*CP-12,521-1 is 4-(6,7-dimethoxyquinazolin-4-yl)
piperazine-1-carboxylic acid isobutyl ester hydrochloride*

FIGURE 1. Structural formula of CP-12,521-1.

MATERIALS AND METHODS

A wedge spirometer (Med-Science Electronics, Model 170) was used which generates 1.0 volt/L and 0.1 volt/L/sec at the electrical outputs for volume and flow respectively. The output signals were recorded on an xy recorder (EAI Model 1100 E Variplotter). Volume data were plotted on the x-axis and flow data on the y-axis of graph paper measuring 11½" by 17", marked at 1/10" intervals. Flow-volume loops are generated in a clockwise direction, the portion below the zero flow line representing inspiration, the upper portion expiration.

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Twenty subjects from 36 patients with a history of bronchospastic disease were studied. Patients were placed at random into two groups. After one week on placebo, each group received either Tedral or CP-12,521-1 for four weeks, after which they were crossed over. Flow-volume loops (FVL) and other pulmonary function data were determined at weekly intervals.¹⁰

RESULTS AND DISCUSSION

Though many respiratory parameters may be derived from both "conventional" spirometry and flow-volume loops, two that are particularly useful for diagnosis of respiratory ailments can only be derived from the latter. These two are: (1) the "effort dependent" and "mechanical property dependent" portions of the ex-

FIGURE 2. A typical flow-volume loop of a normal subject (B.K.J.).

FIGURE 3. Flow-volume loops of an asthmatic during (right) and after (left) an attack.

piratory flow loop which are the γ - β and β - α segments respectively, and (2) the slope of the expiratory portion of the loop. This latter is calculated by dividing the flow rate in L/sec by the 50-75 per cent portion of the forced vital capacity.

Figure 2 indicates a typical flow-volume of a normal subject (B.K.J.), and Figure 3 is representative of an asthmatic (patient no. 5) during and after an attack.

Of the twenty patients studied, three males were excluded because the values for their flow loops placed them in either the normal or the restrictive range.⁶ The remaining seventeen patients comprised three males and fourteen females whose average ages were 18 and 35 years, respectively. For the former, an 8-year history of asthma was elicited and the latter a 15-year history.

Table I presents the data derived from flow-volume loops of the asthmatics during their treatment periods. The number of patients improved is indicated in Table II, and it can be seen that CP-12,521-1 and Tedral were equally effective in the management of this group of asthmatic patients. These data on this smaller selected group confirm the findings derived from studies on these patients with the two drugs Tedral and Hoquizil (a metabolite of CP-12,521-1).¹¹

TABLE I
DATA DERIVED FROM FLOW-VOLUME LOOPS OF ASTHMATICS

	FVC (L)	MEFR (L/sec)	MIFR (L/sec)	Slope*
Females (14)				
placebo				
mean	2.32	2.83	2.30	1.23
SD	0.52	1.07	0.96	0.44
tedral				
mean	2.44	3.14	2.31	1.44
SD	0.49	0.65	0.61	0.38
CP-12,521-1				
mean	2.43	3.20	2.32	1.40
SD	0.83	0.83	0.74	0.42
Males (3)				
placebo				
mean	2.88	3.32	2.84	1.13
SD	1.72	1.27	1.40	0.27
tedral				
mean	2.47	2.86	2.71	1.14
SD	1.45	1.11	1.26	0.51
CP-12,521-1				
mean	2.88	3.85	2.94	1.53
SD	1.43	1.41	1.41	0.97

*Normal (20 volunteers) - 2.82 ± 0.79 , according to Weitzner, Berenyi, and Harmel (1968).

TABLE II
SUMMARY OF TREATMENT COMPARISONS

Treatment comparisons	Number of patients					
	improved*		worsened*		no change	
	M	F	M	F	M	F
CP-12,521-1† to placebo	6	2	3	1	4	0
Tedral to placebo	6	1	1	1	7	1
CP-12,521-1† to Tedral	4	2	5	1	4	0

*10 per cent.

†Only 13 females completed treatment.

SUMMARY

A new oral bronchodilator, CP-12,521-1 was studied in 17 asthmatics. Respiratory flow-volume loops were obtained during an 8-week double-blind randomized crossover study. The usefulness and practicality of this technique in the evaluation of the response of patients to treatment were clearly indicated.

RÉSUMÉ

Un nouveau broncho-dilatateur par voie buccale, le CP-12,521-1, a été étudié chez 17 asthmatiques. On a obtenu des courbes de débit-volume respiratoire au cours d'une étude à double inconnu d'une durée de 8 semaines. L'utilité et l'application pratique de cette technique pour évaluer la réponse des malades à ce traitement sont mises en évidence.

REFERENCES

1. BUTLER, J.; WHITE, H. C.; & MELVITTLE ARNOT, W. The Pulmonary Compliance in Normal Subjects. *Clin. Sc.* 16: 709 (1957).
2. MEAD, J. Mechanical Properties of Lungs. *Physiol. Rev.* 41: 281 (1961).
3. AMBLAVAGAR, M. & ROBERTS, D. V. A Method of Recording Respiratory Pressure Volume Relations in Acute Illness. *Anaesthesia*. 21: 184 (1966).
4. FRY, D. L. & HYATT, R. E. Pulmonary Mechanics: A Unified Analysis of the Relationship between Pressure, Volume and Gas Flow in the Lungs of Normal and Diseased Human Subjects. *Am. J. Med.* 29: 672 (1960).
5. HYATT, R. E.; SCHILDER, D. P.; & FRY, D. L. Relationship between Maximum Expiratory Flow and Degree of Lung Inflation. *J. Appl. Physiol.* 13: 331 (1958).
6. LAPP, N. L. & HYATT, R. E. Some Factors Affecting the Relationship of Maximal Expiratory Flow to Lung Volume in Health and Disease. *Dis. Chest*. 51: 475 (1967).
7. BERENYI, K. J.; WEITZNER, S. W.; TANG, I. P.; & HARMEL, M. H. Effects of Anesthesia and Operation upon Respiratory Flow-Volume Loops. *Anesthesiology*. 29: 174 (1968).
8. WEITZNER, S. W.; BERENYI, K. J.; & HARMEL, M. H. Observations on Respiratory Flow-volume Loops. *Brit. J. Anaesth.* 40: 716 (1968).
9. DERY, D. W. & HENDLER, E. Evaluation of the Respiratory Flow-volume Loop Technic. *Engineering in Medicine and Biology, Proceedings of the 18th Annual Conference, Philadelphia* (1965), p. 90.
10. BERENYI, K. J.; MCFADDEN, R.; LYONS, H.; & STEEN, S. Clinical Trial of a New Oral Bronchodilator (CP-12,521-1). Presented at the Second Portuguese-Brazilian Congress of Anesthesiology, Lisbon, Portugal, September 1-4, 1968.
11. SCILLITANI, B.; THOMAS, J.; BREWER, T. F., III; LYONS, H.; & STEEN, S. N. Hoquizil - A New Oral Bronchodilator: A Double-blind, Randomized, Coded Clinical Study, Using Body Plethysmography. *Proceedings of the Ninth Congress of the Scandinavian Society of Anesthesiologists, Bergen, Norway, June 26-28, 1969. Acta Anaesth. Scandinav. Suppl.* 37: 299 (1970).